Is More Better? Chemotherapy for Patients With Extensive-Stage Small-Cell Lung Cancer

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More is usually better for most of the things that we utilize or consume in our lives. In this issue of the Journal, Pujol et al. (1) report on a study in which they attempted to answer the question of whether more chemotherapy is better for patients with extensive-stage small-cell lung cancer. The answer from their study design in this patient population is that more chemotherapy is better. In their introduction and discussion, Pujol et al. carefully documented that most previous approaches for giving more chemotherapy to patients with extensive small-cell lung cancer have not increased survival. Should their four-drug regimen, which does appear to prolong survival, now be adopted as the new standard treatment for extensive-stage small-cell lung cancer, or is further clinical research needed? I will comment on the toxicity of their four-drug regimen and on the survival of the patients treated on this and other related trials to propose that further clinical research is needed.

The study by Pujol et al. (1) is appropriately designed and clearly reported, and their patient population is well characterized. Before treatment, the patients were thoroughly evaluated for sites of potential metastatic disease with fiberoptic bronchoscopy, computed tomography of the brain, and bone marrow biopsies. The patients were included if they had asymptomatic brain metastases. Thus, it was an inclusive study, with well-characterized patients with extensive-stage small-cell lung cancer.

The authors’ selection of the standard treatment, etoposide plus cisplatin, used doses within the standard ranges currently used around the world. In a previous study (2), the authors found that their four-drug regimen of etoposide, cisplatin, 4′-epidoxorubicin, and cyclophosphamide given every 4 weeks caused longer survival with less toxicity than 20%–50% higher doses of the same drugs with granulocyte—macrophage colony-stimulating factor (GM-CSF) support for patients with extensive-stage small-cell lung cancer. Their current study was designed to show an improvement in 1-year survival of 15%, a somewhat optimistic estimate.

The patients treated with the four-drug regimen had dramatically more hematologic toxicity than the patients treated with the two-drug combination. Ninety-nine percent had grade 3 or 4 neutropenia and two thirds needed intravenous antibiotics when treated with the four-drug regimen compared with 85% and 26% on the two-drug arm, respectively. More importantly, the percentage of toxicity-related deaths reached 9% in the four-drug regimen, while the death rate in the standard arm was a more typical 5.5%.

The study was mature because 196 of the 226 patients had died at the time of the analysis. Despite the increased number of toxicity-related deaths, the median survival in the patients receiving the four-drug regimen was prolonged. These patients lived a median of 10.5 months, 5 weeks longer than the patients treated with the two-drug standard regimen, and they had a similar quality of life. The median survival of 10.5 months for the patients treated with the four-drug regimen in this study, which was performed during the period from March 1996 through March 1999, is comparable to the median survival of 10.8 months in a similar patient population treated with this four-drug regimen by this group in an earlier study, which was done in the period from 1991 through 1994 (2). The median survival of 9.3 months for the patients treated on the control arm (etoposide and cisplatin) of the current study is similar to that seen in other studies of patients with extensive-stage small-cell lung cancer done in North America [reviewed in (3)]. Pujol et al. have posed an important question and show a modest prolongation in survival by increasing the number of drugs given to their patients with small-cell lung cancer.

I have two concerns, however, about the application of this study to the standard treatment of patients with extensive-stage small-cell lung cancer. The first concern is that the investigators used a 4-week cycle rather than a 3-week cycle for etoposide and cisplatin in the control arm. One is left to wonder if similar results could have been achieved by shortening the treatment interval from 4 weeks to 3 weeks for the patients treated with the standard regimen of etoposide and cisplatin. Two recent studies (4,5) performed in the U.K. have examined the impact of shortening the treatment interval with two different combinations of chemotherapy. Patients with both limited-stage and extensive-stage small-cell lung cancers were treated with two different chemotherapy regimens, in which the treatment interval was reduced from 4 weeks to 3 weeks (4) and from 3 weeks to 2 weeks (5). These studies incorporated growth factors (GM-CSF or granulocyte CSF) in their experimental arm. Both of the studies showed a prolongation of survival and similar or reduced toxicity when the treatment cycle was shortened by a week. These studies are not directly analogous to the study by Pujol et al. (1) because most of the patients had limited-stage disease (60% or 77%). The use of these relatively high doses of chemotherapy in these studies did not allow inclusion of concurrent chest radiotherapy in the induction regimen, the standard treatment for patients with limited-stage small-cell lung cancer. The median survival of the patients with limited-stage small-cell lung cancer treated in these two studies was less than 18 months (4,5), shorter than what would be expected for a study population of patients with limited-stage small-cell lung cancer treated with etoposide and cisplatin with concurrent chest radiotherapy (6). Therefore, although the increased dose-rate intensity of the drugs prolonged survival of patients with small-cell lung cancer (4,5), similar or better results could probably have been achieved for patients with limited-stage disease by giving etoposide and cisplatin plus chest radiotherapy.

The second concern is whether the 5-week prolongation of survival in the study by Pujol et al. (1) is worth 67% of their
patient population requiring antibiotic infusions for febrile neutropenia and a 9% treatment-related mortality. This degree of treatment-related toxicity was reproducible in two patient populations because it was similar to that observed in the authors' previous study of patients with extensive-stage small-cell lung cancer treated with a comparable chemotherapy regimen (2). Their previous study also had five (8%) toxicity-related deaths among the 60 patients treated.

The approach of the investigators has been to add two drugs to the standard regimen of etoposide and cisplatin. The addition of agents to a standard regimen of etoposide and cisplatin for patients with extensive-stage small-cell lung cancer has been tested in other trials. The study reported by Loehrer et al. (1) in 1995 added the drug ifosfamide to a 4-day regimen of etoposide and cisplatin. Etoposide and cisplatin were given over a 4-day period rather than the more typical 3-day period. Thus, two different studies (1,7) have now shown that the addition of an alkylating agent with or without 4'-epidoxorubicin prolongs survival albeit with the addition of hematologic toxicity. The findings from these studies have not been widely adopted within the cooperative groups in North America, Europe, or Asia because the control arm in most studies of extensive-stage small-cell lung cancer remains etoposide plus cisplatin.

What can we learn from the study by Pujol et al. (1), and where should we go from here? I do not believe that their four-drug regimen should be adopted as standard treatment at this time. As I previously mentioned, I remain concerned that a 3-week schedule could have resulted in a similar survival. I believe further clinical research is needed before adopting this regimen. For example, the four-drug regimen fits the criteria of the American Society of Clinical Oncology (8) for using hematopoietic colony-stimulating factors because their regimen caused febrile neutropenia in more than 40% of their patients. The inclusion of hematopoietic colony-stimulating factors with the four-drug regimen could reduce the hospitalization rate for febrile neutropenia and fatal toxicity to make the regimen more tolerable. This modification would likely show up as an improved quality of life or prolongation in survival.

The last important question is the potential impact of dose-intensive chemotherapy regimens on the long-term survival of patients with extensive-stage small-cell lung cancer. The prolongation of median survival by 5 weeks in the study by Pujol et al. (1) may not be particularly attractive to this patient population if they spend part of their time in the hospital with febrile neutropenia requiring intravenous antibiotic administration. The current 5-year survival of patients with extensive-stage small-cell lung cancer in the United States is an abysmal 2% (3). If this survival could reach to 5% or even 10%, many patients might opt for treatment with these more toxic regimens. The survival curves in the article by Pujol et al. show an encouraging advantage for the four-drug regimen beyond 2 years, but the results are immature. It will be helpful if the authors could continue to follow their patients and report their outcomes. It may be useful for them to combine data from different studies in a formal meta-analysis to examine the question of whether more is better because it could have an impact on our selection of regimens for patients with extensive-stage small-cell lung cancer.

REFERENCES


