Randomized Trial of Alternating Versus Sequential Radiotherapy/Chemotherapy in Limited-Disease Patients With Small-Cell Lung Cancer

Reviewers: John Han-Chih Chang, MD and Ken Blank, MD

This article details the European Organization for Research and Therapy of Cancer (EORTC) Lung Cancer Cooperative Group's (LCCG) trial on the sequencing of combined modality therapy for limited stage small cell lung cancer.

The National Cancer Institute (NCI) and the Cancer And Leukemia Group B (CALGB) published reports in 1987 (in the Annals of Internal Medicine and the New England Journal of Medicine, respectively) which, randomized trials that demonstrated an improved survival in patients that received thoracic radiation versus those that were only treated with chemotherapy alone. Pignon et al in 1992 published in the New England Journal of Medicine a meta-analysis on 13 randomized prospective trials with limited stage small-cell lung cancer. It demonstrated that there was a modest yet significant overall survival advantage at 3 years -- 14% vs. 9% respectively for those treated with combined modality (i.e. chemotherapy and thoracic radiation therapy) as opposed to chemotherapy alone.

Based upon these trials, advances have attempted to be made in the sequencing of the radiation and chemotherapy to improve the therapeutic ratio. The previously mentioned CALGB trial did approach this timing issue with respect to thoracic radiation. It found that there was no significant difference in overall survival in the patients treated with radiation therapy concurrently with the first cycle of chemotherapy versus those treated concurrently with radiation starting with the fourth (of six total) cycle of chemotherapy. The toxicities were more pronounced when radiation was started with the first cycle chemotherapy. The NCI - Canada and Jeremic et al published randomized prospective studies in the Journal of Clinical Oncology (JCO) in 1993 and 1997, respectively. They both reported significant progression and/or recurrence free and overall survival advantages with beginning thoracic radiation therapy concurrent with the first cycle of chemotherapy.

This EORTC-LCCG study enrolled 335 patients, who were randomized to sequential chemotherapy and radiation therapy versus alternating schedule chime/radiation therapy. The sequential therapy (S group) patients received Cyclophosphamide (Cytoxan)/Doxorubicin (Adriamycin)/Etoposide (VP-16) or CDE chemotherapy for five cycles (a cycle every three weeks) followed by thoracic radiation (5000 rads in 20 fractions) two weeks after the first day of the last chemotherapy cycle. The alternating schedule (A group) patients received the same type and dose of chemotherapy, but on a different schedule when combined with the same dose of radiation therapy. CDE was given for one cycle every four weeks with radiation delivered in four one week (1250 rads in five fractions) treatments between cycles two and three, three and four, four and five, and finally after cycle five. Thus, there were three-week intervals between radiation treatment weeks. Because of the hematologic toxicity of the treatment to the bone marrow, the patients in the A group received 25% less chemotherapy dose than the S group. Complications of esophagitis, esophageal stenosis, and lung fibrosis were 3%, 1%, and 38% respectively and not significantly different between the two groups. As alluded to above, significant decreases in white blood cell and platelet counts were more severe in group A than in group S (90% versus 77% and 33% versus 20%, respectively).

Median follow-up was 43 months. Median overall survival was 15 months. The results revealed no significant survival advantage between the two treatment schemes. One year overall survival was 60% in A and 64% in S. Two year overall survival was 26% in A and 23% in S. Three year overall survival was 12% in the A group and 15% in the S group.

This study was a "negative" trial, because it revealed no survival advantage. Many factors could explain why this was the case. The fact that patients in the A group due to treatment related toxicities received only 75% of the chemotherapy dose that the patients in the S group could be a legitimate reason. Also, given that there was so much time in between the one-week
radiation treatments could allow the tumor cells to repopulate and repair despite the chemotherapy. In support of this contention, Komaki et al published a prospective randomized trial in the 1995 International Journal of Radiation Oncology Biology and Physics that compared interdigitating (similar to the alternating schedule) chemo/radiation therapy with concurrent chemo/radiation therapy (radiation was initiated with the first cycle of chemotherapy and continued to its completion continuously five days a week). The patients who received concurrent therapy had a significant survival advantage at one through four years from diagnosis.

Does this mean that sequential is the way to treat these patients? It is an established method of thoracic radiation timing, but as reported in other articles (some mentioned above), concurrent chemo/radiation therapy seems to be most advantageous in treating limited stage small cell lung cancer provided that patients are able to tolerate therapy. As with any cancer treatment, one must individualize therapy based on the patient's performance status and the extent of disease.

For more information concerning the treatment of limited small cell lung cancer, please see OncoLink's Small Cell Lung Cancer Menu.