Palliative Hypofractionated Radiotherapy For Non–Small Cell Lung Cancer (NSCLC) Patients Previously Treated By Induction Chemotherapy: Is It For Many, Some, All, Or None?

Timothy D. Wagner, MD, MBA

Approximately 30% of patients with non-small cell lung cancer present with locally advanced disease that is surgically unresectable (1). In patients with adequate performance status, many current practice guidelines recommend that these patients be treated with a combination of chemotherapy and external beam irradiation (2). Over the last several years, the use of chemotherapy with radiation has been supported by several phase III multi-institutional randomized studies, with patients diagnosed with locally advanced NSCLC, having a better progression-free (PFS) and overall survival (OS) when treated with combination therapy than with radiation alone (3, 4). Despite improvements in outcome, results remain modest with aggressive combined modality therapy, with 2 and 5 year survivals in the range of 30% and 20%, respectively (4, 5). In addition, these combined modality approaches are associated with significant toxicity in a patient population that in many cases is already limited in terms of functional reserve before they even initiate definitive therapy. Despite curative efforts, many patients have disease progression or are overly symptomatic either from treatment or from their disease. It could be argued that for certain locally advanced patients, aggressive systemic and local treatment causes more harm than good.

In this issue of the *Journal of Thoracic Disease*, Plataniotis et al. report their results utilizing palliative hypofractionated radiotherapy in a certain subgroup of patients with locally advanced NSCLC who had been treated with induction systemic chemotherapy (6). The radiation treatment regimen delivers 17 Gray (Gy) in 2 fractions of 8.5 Gy per fraction. If one assumes an α/β of 2 for late responding tissues, 17 Gy in 2 fractions is the radiobiologic equivalent of 45 Gy in 25 fractions or 36 Gy in 12 fractions by the linear-quadratic formula (7). It use in the palliative setting for patients with advanced NSCLC is well-described by the current authors and others internationally, where it has compared favorably with other regimens in terms of palliation (8-10). To date, the majority of the published experience with this dosing regimen has been in the advanced, and often metastatic, setting, where it was delivered as monotherapy in previously untreated patients for symptom palliation. It has proved to be an effective regimen for palliation of many symptoms associated with advanced lung cancer such as cough, pain, hemoptysis, and dyspnea.

In their current study, Plataniotis et al., present retrospective results of 28 patients with either stage IIIA or IIIB NSCLC who were treated with a combination of induction chemotherapy followed by hypofractionated radiation therapy (17 Gy in 2 fractions). This hypofractionated regimen was reserved for patients who had locally progressive or non-responding disease, progressive symptoms (pain, dyspnea, cough, hemoptysis), worsening performance status, weight loss of >10% in the past 3 months, or the presence of a symptomatic pleural effusion (7). Among those treated with radiation therapy, the median Karnofsky Performance Status (KPS) was 80, with a median age of 70 years, and 50% (14/28) of patients having stage IIIA or lower disease. There was a reduction in Total

Radiation Oncology Service, Department of Radiology, Brooke Army Medical Center

Disclosure: The author declares no conflicts of interest.

Address for correspondence: Timothy D. Wagner, MD, MBA, Major, Medical Corps, United States Army, Radiation Oncology Service, Department of Radiology, Brooke Army Medical Center. 3851 Roger Brooke Dr., Fort Sam Houston, TX 78234. Tel: +210 916-5046; Fax: +210 916-0330. Email: timothy.d.wagner@us.army.mil or timothywagner@hotmail.com

ISSN: 2072-1439/$ - see front matterr

Symptom Score (TSS) in 68% (19/28) of patients following radiation. Overall survival for the entire cohort was found to be 9 months, with a 1-year survival of 29.8%. No cases of grade 3 or higher esophagitis were reported, with pneumonitis documented in 7% (2/28).

Overall, this treatment strategy appears well tolerated and offers substantial palliation in the majority of patients treated. The question becomes for which patients should such a strategy be considered, and for which patients would a more aggressive treatment approach be warranted. While outcomes in locally advanced NSCLC are relatively poor, studies have shown there are long-term survivors with aggressive combined modality (3, 4). In evaluating the current study, univariate analysis revealed that smaller tumor volume (< 120 cm^3), response to induction chemotherapy (minimal response vs. all others), and KPS (>70) were all significant parameters for survival. A previous comparison of this hypofractionated approach vs. a more protrated regimen (39 Gy in 13 fractions) in patients with advanced NSCLC demonstrated that a more protracted regimen improved OS and freedom from metastatic disease at a cost of increased acute toxicity and slower palliation (10). And while acute toxicity was increased psychological stress among those receiving 39 Gy in 13 fractions was found to be lower. It is quite possible that these patients with smaller tumor volumes and better performance status could have tolerated a more prolonged radiation course, and the evidence suggests that this strategy may increase their chances for long-term survival and reduce stress albeit with the risk of increased acute toxicity.

In the current analysis, all patients received induction chemotherapy with the intent to treat with concurrent chemotherapy and radiation or radical radiation alone thereafter should they have had a response to therapy and not developed any worsening symptoms. Vokes et al. recently published their results of a phase III study evaluating induction chemotherapy followed by concurrent chemoradiation vs. concurrent chemoradiation in patients with locally advanced NSCLC. Investigators found that the addition of induction chemotherapy added toxicity but no survival benefit over concurrent chemoradiation alone (11). Therefore, perhaps those patients with locally advanced NSCLC with adequate performance (KPS >70) and tumor volumes that can be adequately dosed with radiation with acceptable doses to adjacent normal tissue should be strongly considered for definitive concurrent chemoradiation immediately upon completion of staging. With emerging radiation technologies such as respiratory gating, 4-dimensional planning, and daily image-guidance, the therapeutic ratio of protracted courses of thoracic radiation and chemotherapy should theoretically improve (12). In addition, with the advent of functional imaging such as positron emission tomography (PET) and more advanced magnetic resonance imaging (MRI) techniques, pre-treatment evaluation continues to improve in terms of detecting occult disease allowing for more accurate staging and appropriate treatment. This strategy would serve to remove the concern for disease progression or symptom development during the time of induction chemotherapy when there is no local therapy.

For those patients thought to be at high-risk for morbidity from concurrent chemoradiation either because of performance status, disease burden, or symptoms, a sequential approach is a reasonable alternative. And in those patients then progressing on induction chemotherapy, developing worsening symptoms, or experiencing declining performance status, plans for protracted radiation therapy should be reconsidered and this hypofractionated regimen should be entertained. It has been proven to be effective for palliation and convenient for patients with advanced disease, and in the current study has been shown to be safe following systemic therapy.

References

1. Lee CB, Stinchcombe TE, Rosenman JG, Socinski MA. Therapeutic advances in local-regional therapy for stage III non-small-cell lung cancer: evolving role of dose-escalated conformal (3-dimensional) radiation therapy. Clin Lung Cancer 2006; 8: 195-202.
2. Pfister DG, Johnson DH, Azzoli CG, Sause W, Smith TJ, Baker S Jr et al. American Society of Clinical Oncology treatment of unresectable non-small cell lung cancer guideline: Update 2003. J Clin Oncol 2004; 22: 330-53.
3. Marino P, Preatoni A, Cantoni A. Randomized trials of radiotherapy alone versus combined chemotherapy and radiotherapy in stages IIIa and IIIb non-small cell lung cancer: A metaanalysis. Cancer 1995; 76: 593-601.
4. Dillman RO, Herndon J, Seagren SL, Eaton WL Jr, Green MR. Improved survival in stage III non small cell lung cancer: seven year follow up of Cancer and Leukemia Group B (CALGB) 8433 trial. J Natl Cancer Inst 1996; 88:1210-5.
5. Albain KS, Crowley JJ, Turrisi AT III, Gandara DR, Farrar WB, Clark JI et al. Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: A Southwest Oncology Group Phase II Study, SWOG 9019. J Clin Oncol 2002; 20: 3454-60.
6. Plataniotis GA, Theofanopoulou MA, Sotiriadou K, Theodorou K, Mavroidis P, Kyrgias. Palliative hypofractionated radiotherapy for non -small -cell lung cancer (NSCLC) patients previously treated by induction chemotherapy. J Thorac Dis 2009; 1: 5-10.
7. Cross CK, Berman S, Buswell L, Johnson B, Baldini EH et al. Prospective study of palliative hypofractionated radiotherapy (8.5 Gy x 2) for patients with symptomatic non-small-cell lung cancer. Int Jour Radiat Oncol Biol Phys 2004; 58:1098-105.
8. Plataniotis GR, Kouvaris JR, Dardoufas C, Kouloulias V, Theofanopoulou MA, Vlahos L. A short radiotherapy course for locally advanced non-small cell lung cancer (NSCLC). Effective palliation and patients' convenience. Lung Cancer 2002; 35: 203-7.
9. Anonymous. Inoperable non-small-cell lung cancer (NSCLC): a Medical Research Council randomized trial of palliative radiotherapy with two fractions or ten fractions. Report to the Medical Research Council by its Lung Cancer Working Party. Br J Cancer 1991; 63: 265-70.
10. Macbeth FR, Bolger JJ, Hopwood P, Bleehen NM, Cartmell J, Girling DJ, et al., for the Medical Research Council Lung Cancer Working Party. Randomised trial of palliative two-fraction versus more intensive 13-frac-tion radiotherapy for patients with inoperable non-small cell lung cancer and good performance status. Clin Oncol 1996;8:167-75.
11. Vokes EE, Herndon JE II, Kelley MJ, Cicchetti MG, Ramnath N, Neill H et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III non-small-cell lung cancer: Cancer and Leukemia Group B. J Clin Oncol 2007; 25: 1698-704.
12 Keall P, Vedam S, George R, Bartee C, Siebers J, Lerma F et al. The clinical implementation of respiratory-gated intensity-modulated radiotherapy. Med Dosim. 2006; 31: 152-62.