Body Mass Index and Its Association with Clinical Outcomes for Advanced Non–Small-Cell Lung Cancer Patients Enrolled on Eastern Cooperative Oncology Group Clinical Trials

Suzanne E. Dahlberg, PhD, Joan H. Schiller, MD,† Philip B. Bonomi, MD,‡ Alan B. Sandler, MD,§ Julie R. Brahmer, MD,‖ Suresh S. Ramalingam, MD,¶ and David H. Johnson, MD#*

Introduction: Obesity increases the risk of death from many adverse health outcomes and has also been linked with cancer outcomes. The impact of obesity on outcomes of advanced non–small-cell lung cancer patients is unclear.

Methods: The authors evaluated the association of body mass index (BMI) and outcomes in 2585 eligible patients enrolled in three consecutive first-line trials conducted by the Eastern Cooperative Oncology Group. BMI was categorized as underweight (BMI < 18.5 kg/m^2), normal weight (BMI: 18.5 to < 25 kg/m^2), overweight (BMI: 25 to < 30 kg/m^2), and obese (BMI ≥ 30 kg/m^2). In addition to analyzing overall and progression-free survival, reasons for treatment discontinuation were also assessed by BMI group.

Results: Of the patients enrolled, 4.6% were underweight, 44.1% were normal weight, 34.3% of patients were classified as overweight, and 16.9% were obese. Nonproportional hazards existed for obese patients relative to the other three groups of patients, with a change in overall survival hazard occurring at approximately 16 months. In multivariable Cox models, obese patients had superior outcomes earlier on study compared with normal/overweight patients 0.86 (HR=0.86, p=0.04; 95% CI: 0.75–0.99), but later experienced increased hazard (HR=1.54, p< 0.001; 95% CI: 1.22–1.94), indicating a time effect while undergoing treatment.

Conclusion: Data from these three trials suggest differential outcomes associated with BMI, and additional studies of the mechanisms underlying this observation, as well as dietary and lifestyle interventions, are warranted to help optimize therapy.

Key Words: Body mass index, Weight, Obesity, Non–small-cell lung cancer, Advanced disease, First-line therapy, Phase III, Chemotherapy, Bevacizumab.

(*J Thorac Oncol.* 2013;8: 1121-1127)

Elevated body mass index (BMI), defined as weight in kilograms divided by the square of the height in meters, increases the risk of death from many adverse health outcomes and continues to remain a significant public health problem in developed nations such as the United States, Canada, and Europe.[1] BMI-defined overweight and obesity, which affect nearly two thirds of the U.S. population and continue to increase in prevalence, are associated with increased risk of cardiovascular disease, diabetes, arthritis, and asthma, as well as colon, breast, endometrial, and renal cancers.[2–6] With respect to lung cancer, however, many investigations have demonstrated an inverse association between BMI and risk of fatal lung cancers.[7–18]

Despite the wealth of literature detailing the association between BMI and lung cancer incidence, studies evaluating the relationship of BMI on outcomes for patients with lung cancer are somewhat limited.[19] To our knowledge these studies have not focused on lung cancer patients enrolled in clinical trials, which select for patients with fewer comorbidities by way of their eligibility criteria; trials typically require good performance status (PS), adequate organ function, and limited exposure to major surgery or treatments within a reasonable timeframe of study entry. Increased BMI has also been associated with improved outcomes for patients with renal cell cancer and diffuse large B-cell lymphoma, but with poorer prognosis in patients with colon, prostate, and breast cancers.[3,20–22] It is therefore of interest to study whether or not the association between BMI and clinical outcomes can be validated in this setting.

The current study presents results from an analysis of the clinical course of advanced non–small-cell lung cancer (NSCLC) patients enrolled in the most recent three front-line phase III trials, E5592, E1594, and E4599, conducted

*Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, Massachusetts; †Division of Hematology-Oncology, University of Texas Southwestern Medical Center, Dallas, Texas; ‡Department of Medical Oncology, Rush University Medical Center, Chicago, Illinois; §Division of Hematology and Medical Oncology, Oregon Health and Science University, Portland, Oregon; ‖Department of Medical Oncology, Johns Hopkins University, Baltimore, Maryland; ¶Department of Hematology and Medical Oncology, Winship Cancer Institute of Emory University, Atlanta, Georgia; and Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas.

Disclosure: The authors declare no conflict of interest.

Address for correspondence: Suzanne E. Dahlberg, PhD, Department of Biostatistics and Computational Biology, CLSB 11007, Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215. E-mail: dahlberg@jimmy.harvard.edu

ISSN: 1556-0864/13/0809-1121

TABLE 1. Eastern Cooperative Oncology Phase III First-Line Trials in Advanced Non–Small-Cell Lung Cancer, 1993–2004

Study	Regimens	Accrual Period	No. of Patients with BMI Data
E5592: Bonomi et al., 2000	Cisplatin (75 mg/m^2) + etoposide (100 mg/m^2)	1993–94	574
	Cisplatin (75 mg/ m^2) + paclitaxel (250 mg/m^2)		
	Cisplatin (75 mg/ m^2) + paclitaxel (135 mg/m^2)		
E1594: Schiller et al., 2002	Cisplatin (75 mg/ m^2) + paclitaxel (135 mg/m^2)	1996–99	1161
	Cisplatin (100 mg/ m^2) + gemcitabine (1000 mg/ m^2)		
	Cisplatin (75 mg/ m^2) + docetaxel (75 mg/ m^2)		
	Carboplatin, AUC 6.0 mg/ml/min + paclitaxel (225 mg/ m^2)		
E4599: Sandler et al. 2006	Carboplatin, AUC 6.0 mg/ml/min + paclitaxel (200 mg/m^2) + bevacizumab (15 mg/kg)	2001–04	850
	Carboplatin, AUC 6.0 mg/ml/min + paclitaxel (200 mg/m^2)		

AUC, area under the curve; BMI, body mass index.

by the Eastern Cooperative Oncology Group (ECOG) in this patient population. Statistical endpoints included overall survival (OS), progression-free survival (PFS), best objective response, toxicity, and time to treatment discontinuation. To our knowledge, this study is the first to analyze these data using prospectively collected treatment and eligibility criteria and to include detailed information on underweight patients.

PATIENTS AND METHODS

Study Population

During the period from 1993 to 2004, the ECOG enrolled 2684 patients to three phase III trials of first-line systemic chemotherapy for advanced NSCLC. In brief, eligible patients had stage IIIB, IV, or recurrent disease, ECOG PS 0 to 1, no prior systemic chemotherapy, and adequate bone marrow, hepatic, and renal function. Per protocol, all patients were dosed based on actual weight. Additional details regarding eligibility, treatment, and results have been reported elsewhere and are summarized in Table 1; E1594 enrolled 65 eligible patients with PS 2 before a protocol amendment restricted eligibilty to ECOG PS of 0 or 1 only.[23–25] The primary endpoint of these trials was OS, and the primary analyses were conducted among all eligible patients. Each participant gave informed consent. These studies were conducted in accordance with the Declaration of Helsinki, current Food and Drug Administration Good Clinical Practices, and local institutional review board requirements.

Statistical Methods

Baseline patient demographics and disease characteristics were compared using Fisher's exact test. OS, the primary endpoint considered, was defined as time interval in months from randomization to death from any cause. PFS was defined as the time interval in months from randomization to documented progression or death. Patients not experiencing an event were censored at the last date of follow-up for OS and the last date of disease assessment for PFS. Time-to-event distributions were estimated using the Kaplan–Meier method, and comparisons of these distributions were made using the log-rank test.[26] Multivariable piecewise Cox proportional hazards models were used to estimate hazard ratios (HRs) for OS and PFS.[27] Response and toxicity on protocols E5592 and E1594 were assessed using ECOG criteria; for E4599, the Response Evaluation Criteria in Solid Tumors version 1.0 and Common Terminology Criteria for Adverse Events version 2.0 were used. The cumulative incidence function of time to treatment discontinuation because of toxicity, adjustment for death, progression, and withdrawal/other as competing events was constructed using the method of Kalbfleish and Prentice.[28] All p values are two-sided, confidence intervals (CIs) are at the 95% level, and no adjustments have been made for multiple comparisons.

BMI at the time of randomization was defined as weight in kilograms divided by the square of the height in meters. Patients were stratified into BMI groups defined by the World Health Organization: underweight (BMI < 18.5 kg/m^2), normal weight (BMI: 18.5 to < 25 kg/m^2), overweight (BMI: 25 to < 30 kg/m^2), and obese (BMI ≥ 30 kg/m^2).[20,29]

RESULTS

At a median follow-up of 64.9 months, 2585 of the 2684 patients (96.3%) randomized on these trials were declared eligible and constituted the primary analysis population; all had BMI measurements at the time of study registration. Table 2 displays the baseline patient demographics and disease characteristics of the study cohort by BMI group. Consistent with the general population, 4.6% of patients were underweight, 44.1% were normal weight, 34.3% of patients were classified as overweight, and 16.9% were obese. Most of the baseline demographics and disease characteristics were significantly imbalanced by BMI group, with the exception of stage, histology, prior surgery, pleural involvement, liver metastases, and baseline serum albumin. Underweight patients were more likely to be younger, African American, female, have worse ECOG PS, have more weight loss and radiotherapy before study enrollment, and be enrolled on the more recent trials.

Figure 1 displays the results of the OS analysis by BMI group. Of 2585 patients, 2353 (91%) had died at the time of this analysis. The median OS estimated among underweight patients was 7.0 months (95% CI: 5.5–9.6), among normal-weight patients was 8.6 months (95% CI: 8.0–9.4), among overweight patients was 9.3 months (95% CI: 8.6–10.1), and among obese patients was 11.0 months (95% CI: 10.2–11.9).