Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 4, pp. e269–e274, 2011

0360-3016/$ - see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2011.01.056

CLINICAL INVESTIGATION **Lung**

PULMONARY TOXICITY IN STAGE III NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH HIGH-DOSE (74 GY) 3-DIMENSIONAL CONFORMAL THORACIC RADIOTHERAPY AND CONCURRENT CHEMOTHERAPY FOLLOWING INDUCTION CHEMOTHERAPY: A SECONDARY ANALYSIS OF CANCER AND LEUKEMIA GROUP B (CALGB) TRIAL 30105

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Purpose: **Cancer and Leukemia Group B (CALGB) 30105 tested two different concurrent chemoradiotherapy platforms with high-dose (74 Gy) three-dimensional conformal radiotherapy (3D-CRT) after two cycles of induction chemotherapy for Stage IIIA/IIIB non–small cell lung cancer (NSCLC) patients to determine if either could achieve a primary endpoint of >18-month median survival. Final results of 30105 demonstrated that induction carboplatin and gemcitabine and concurrent gemcitabine 3D-CRT was not feasible because of treatment-related toxicity. However, induction and concurrent carboplatin/paclitaxel with 74 Gy 3D-CRT had a median survival of 24 months, and is the basis for the experimental arm in CALGB 30610/RTOG 0617/N0628. We conducted a secondary analysis of all patients to determine predictors of treatment-related pulmonary toxicity.**

Methods and Materials: **Patient, tumor, and treatment-related variables were analyzed to determine their relation with treatment-related pulmonary toxicity.**

Results: **Older age, higher N stage, larger planning target volume (PTV)1, smaller total lung volume/PTV1 ratio, larger V20, and larger mean lung dose were associated with increasing pulmonary toxicity on univariate analysis. Multivariate analysis confirmed that V20 and nodal stage as well as treatment with concurrent gemcitabine were associated with treatment-related toxicity. A high-risk group comprising patients with N3 disease and V20 >38% was associated with 80% of Grades 3-5 pulmonary toxicity cases.**

Conclusions: **Elevated V20 and N3 disease status are important predictors of treatment related pulmonary toxicity in patients treated with high-dose 3D-CRT and concurrent chemotherapy. Further studies may use these metrics in considering patients for these treatments.** **© 2011 Elsevier Inc.**

Chemoradiotherapy, 3D conformal radiotherapy, Non–small cell lung cancer, Pulmonary toxicity.

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The following institutions participated in this study: Christiana Care Health Services, Inc. CCOP, Wilmington, DE: Stephen Grubbs, M.D., supported by CA45418; Duke University Medical Center, Durham, NC: Jeffrey Crawford, M.D., supported by CA47577; Kansas City Community Clinical Oncology Program CCOP, Kansas City, MO: Jorge C. Paradelo, M.D.; Roswell Park Cancer Institute, Buffalo, NY: Ellis Levine, M.D., supported by CA02599; University of California at San Diego, San Diego, CA: Joanne Mortimer, M.D., supported by CA11789; University of Minnesota, Minneapolis, MN: Bruce A Peterson, M.D., supported by CA16450; University of Missouri/Ellis Fischel Cancer Center, Columbia, MO: Michael C Perry, M.D., supported by CA12046; Wake Forest University School of Medicine, Winston-Salem, NC: David D Hurd, M.D., supported by CA03927; Southeast Cancer Control Consortium Inc. CCOP, Goldsboro, NC: James N. Atkins, M.D., supported by CA45808; University of North Carolina at Chapel Hill, Chapel Hill, NC: Thomas C. Shea, M.D., supported by CA47559; University of Massachusetts Medical School, Worcester, MA: William V. Walsh, M.D., supported by CA37135.

Conflict of interest: none.

Acknowledgment—The authors would like to acknowledge the assistance of Fran Laurie and Donna Wardle for their assistance at Quality Assurance Review Center.

Received Oct 1, 2010, and in revised form Dec 20, 2010. Accepted for publication Jan 18, 2011.

INTRODUCTION

Lung cancer remains the leading cause of cancer mortality. Approximately 85% of lung cancer patients have non–small cell lung cancer (NSCLC) histology, and one-third of NSCLC patients present with Stage IIIA or IIIB disease. For patients with preserved performance status and adequate organ function, the combination of chemotherapy and radiation therapy is the standard of care (1, 2). Concurrent chemoradiotherapy results in improved survival compared with sequential chemotherapy and radiation (3).

The development of three-dimensional conformal radiotherapy (3D-CRT) planning techniques has led to improved radiation delivery facilitating better tumor coverage, compared with conventional techniques, while minimizing exposure of surrounding normal tissues (4–7). The ability for 3D-CRT to decrease normal organ radiation exposure led several investigators to perform Phase I and II trials of escalated dose 3D-CRT either alone or in combination with chemotherapy in NSCLC (8–15).

Cancer and Leukemia Group B (CALGB) 30105 was a two-arm randomized Phase II trial investigating induction and concurrent chemotherapy with 3D-CRT to 74 Gy. Arm A investigated induction and concurrent chemotherapy with carboplatin and paclitaxel, and arm B investigated induction chemotherapy with carboplatin and gemcitabine followed by single-agent concurrent gemcitabine and 3D-CRT (16). Arm B was closed prematurely due to a high rate of Grade 4–5 pulmonary toxicity. We performed this secondary analysis to investigate the correlation between baseline pulmonary function and radiation treatment planning parameters as risk factors for pulmonary toxicity in patients treated with concurrent chemotherapy and 74 Gy 3D-CRT.

METHODS AND MATERIALS

Eligibility

CALGB 30105 eligibility criteria have been published previously (16). Briefly, patients with histologically or cytologically confirmed Stage IIIA-IIIB (American Joint Committee on Cancer 2000) unresectable NSCLC, Eastern Cooperative Oncology Group performance status (PS) of 0-1, and normal organ and marrow function were eligible. Patients with direct invasion of the vertebral bodies or scalene, supracalvicular, or contralateral hilar adenopathy were ineligible. All patients were required to have a forced expiratory volume in 1 second (FEV1) of >1.2 L. After giving informed consent, patients were randomized to treatment arm A or B (Fig. 1). The trial was approved by the institutional review boards of the participating institutions.

Chemotherapy treatment plan

Patients in arm A received induction chemotherapy with carboplatin area under the curve (AUC) of 6 using the Calvert equation (17) and paclitaxel 225 mg/m^2 on days 1 and 22. On day 43, patients received weekly carboplatin AUC = 2 and paclitaxel 45 mg/m^2 for 7 weeks concurrent with 3D-CRT. Patients in arm B received induction chemotherapy carboplatin AUC = 5 using the Calvert equation on days 1 and 22, and gemcitabine 1,000 mg/m^2 on days 1, 8, 22, and 29. On day 43, patients received twice weekly gemcitabine 35 mg/m^2 for 7 weeks concurrently with 3D-CRT. Details of premedication, dose modifications, and chemotherapy treatment delays have been published previously (16).

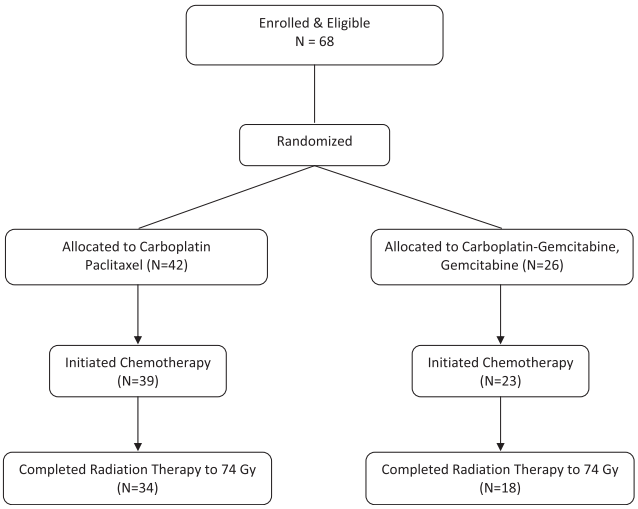

Fig. Consort diagram.

Radiation treatment plan

Before induction chemotherapy, all patients underwent contrast-enhanced computed tomography (CT) based radiation treatment planning in customized immobilization devices. For the first phase of treatment, the primary tumor and pathologically involved adenopathy (those with a necrotic center, biopsy proven, FDG-positron emission tomography avid, or measuring >1 cm in short-axis diameter) were contoured on each slice of the planning CT as gross tumor volume (GTV1). Clinical target volume 1 (CTV1) was created by expanding GTV1 by 2 cm in all directions except for the interface of the primary tumor and normal lung parenchyma where it was expanded 0.5 cm or more at the discretion of the treating radiation oncologist. Additionally, elective treatment of ipsilateral upper paratracheal and contralateral lower paratracheal nodal stations for T2N2 patients or lower paratracheal and subcarinal regions for T3N1 patients could be included in CTV1. Planning target volume (PTV1) was created by expanding CTV1 by 1 cm in all directions. For the second phase of treatment, at the discretion of the treating radiation oncologist, GTV2 could be redefined as the reduced GTV volume following induction chemotherapy. For patients not responding to induction chemotherapy GTV2 was identical to GTV1. CTV2 and PTV2 were created by sequential expansions similar to the first course. For both courses, the lungs, heart, and spinal cord were contoured on each planning CT slice.

3D-CRT was required for this study. Beam arrangements and treatment portals were chosen to maximize tumor coverage and minimize normal tissue exposure. Photon beam energies of 4 MV or higher were required. The prescription radiation dose for the first course was 40 Gy in 2 Gy daily fractions to PTV1, followed by 34 Gy in 2 Gy daily fractions to PTV2. Radiation dose was prescribed to isocenter and accounted for tissue heterogeneity. Radiation planning required that 100% of the PTV be encompassed by the 95% isodose surface and no more than 10% of the volume received more than 110% of the prescription dose. The protocol mandated that the maximum dose to the spinal cord be 49 Gy, and, wherever possible, without shielding gross tumor, the dose to the lung parenchyma, esophagus, and heart should be minimized. No specific dose–volume constraints were placed on the lung, heart, and