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Prophylactic cranial irradiation in elderly patients with small cell lung cancer: Findings from a North Central Cancer Treatment Group pooled analysis

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ABSTRACT

Objectives: To examine the efficacy of prophylactic cranial irradiation (PCI) in elderly patients with small cell lung cancer (SCLC) (≥70 years of age) from a pooled analysis of four prospective trials.

Materials & Methods: One hundred fifty-five patients with SCLC (limited stage, LSCLC, and extensive stage, ESCLC) participated in four phase II or III trials. Ninety-one patients received PCI (30 Gy/15 or 25 Gy/10) and 64 patients did not receive PCI. Survival was compared in a landmark analysis that included only patients who had stable disease or better in response to primary therapy.

Results: Patients who received PCI had better survival than patients who did not receive PCI (median survival 12.0 months vs. 7.6 months, 3-year overall survival 13.2% vs. 3.1%, HR = 0.53 [95% CI 0.36–0.78], $p = 0.001$). On multivariate analysis of the entire cohort, the only factor that remained significant for survival was stage (ESCLC vs. LSCLC, $p = 0.0072$). In contrast, the multivariate analysis of patients who had ESCLC revealed that PCI was the sole factor associated with a survival advantage (HR = 0.47 [95% CI 0.24–0.93], $p = 0.03$). Grade 3 or higher adverse events (AEs) were significantly greater in patients who received PCI (71.4% vs. 47.5%, $p = 0.0031$), with non-neuro and non-heme being the specific AE categories most strongly correlated with PCI delivery.

Conclusions: PCI was associated with a significant improvement in survival for our entire elderly SCLC patient cohort on univariate analysis. Multivariate analysis suggested that the survival advantage remained significant in patients with ESCLC. PCI was also associated with a modest increase in grade 3 or higher AEs.

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1. Introduction

Prophylactic cranial irradiation (PCI) is standard therapy in the management of patients with limited stage small cell lung cancer (LSCLC) or extensive stage small cell lung cancer (ESCLC) who have experienced any degree of favorable response to initial therapy.[1–7] In spite of the proven survival benefit, many eligible patients with SCLC do not receive PCI due to patient or physician concerns regarding neurotoxicity. In clinical practice, the dilemma of whether to administer this life-prolonging therapy is most controversial in older individuals. Lung cancer is a disease which is prevalent in the elderly, with a median age at diagnosis of approximately 70 years. Unfortunately, most of the trials that have led to the adoption of PCI enrolled relatively few elderly patients. The risk benefit analyses for these patients are particularly challenging as the survival benefit for PCI was seen at 1 year following PCI for LSCLC,[2] although much sooner in ESCLC.[4] Previously, we analyzed the effect of PCI in a large cohort of patients with both LSCLC and ESCLC, confirming the benefit in both patient populations.[3] The purpose of this study was to specifically examine the results of PCI in patients with SCLC (both LSCLC and ESCLC) who are elderly (≥70 years) in order to evaluate whether the survival benefit from PCI is also present in older patients.

2. Materials & Methods

The patient population included patients 70 years of age or older with LSCLC or ESCLC who participated in four prospective phase II or III North Central Cancer Treatment Group trials (86–20–51, 89–20–51, 89–20–52, 95–20–53). Patients with stable disease or better following chemotherapy +/– thoracic radiotherapy (TRT) were included. Response assessment was based on history and physical examination, chest radiographs (86–20–51 and 89–20–51) and computed tomography (CT) scans (89–20–52 and 95–20–52). All patients had ECOG performance scores ranging from 0 to 2. Regarding the delivery of PCI, study guidelines differed slightly. In 86–20–51, ESCLC patients were to receive TRT and PCI (30 Gy/15) if they had a complete response outside of the chest. All patients with LSCLC were to receive TRT and PCI (30 Gy/15) if they had stable disease or a better response to the initial therapy (chemotherapy). Trial 89–20–51 and trial 89–20–52 included only patients with ESCLC or LSCLC, respectively, who were to receive PCI (30 Gy/15) if a complete response after initial therapy was achieved. Trial 95–20–53 included only patients with LSCLC who were to receive PCI after any response to initial therapy. Only 95–20–53 utilized the most common current PCI regimen (25 Gy/10), which was administered after initial chemotherapy but before TRT. All trials specified brain imaging (contrast-enhanced CT or MRI) at the time of initial staging as well as prior to the delivery of PCI in order to exclude patients with metastatic disease already present in the brain. Patients had follow-up performed as dictated by the trial in which they were enrolled. Institutional Review Boards at the study sites had approved these trials and all participants provided written informed consent. See Table 1 for further information regarding the details of the four individual trials.

3. Statistical Methods

Baseline patient and disease characteristics between the PCI and no-PCI groups were compared utilizing the chi-square test for categorical data and the Wilcoxon rank sum test for continuous data. Survival was compared using a landmark analysis that included only patients who had stable disease (SD) or better. Overall survival (OS) from the landmark time was assessed for the PCI and no-PCI groups, where the landmark time was the point in time at which the patients could have started PCI per their particular treatment protocol. The Kaplan–Meier method was used to compare the survival distributions for the two groups. The Cox proportional hazards model was utilized for both the univariate and multivariate analyses. The multivariate models were developed by including PCI (vs. no-PCI) and all the clinically relevant factors that were collected across all trials. These included age, gender, ECOG PS, and stage. We also further adjusted for complete response to chemotherapy to take into account the association between receipt of PCI and response to chemotherapy. Score and likelihood ratio p values were reported for the univariate and multivariate models, respectively, after stratifying by study, which takes into account key differences between the trials. The Wald test was used to examine the significance of parameters with more than two categories. Hazard ratios (HRs) and their associated 95% confidence intervals (CIs) were calculated for univariate and multivariate results. Chi-square or Fisher's exact tests were used to compare the adverse event rates between PCI and no-PCI groups, focusing on the grade 3 or higher adverse events. In addition, univariate logistic regression models were also used to assess the relationship between PCI (vs. no-PCI) and grade 3 or worse adverse events, after stratifying by study. All tests were two-sided, with p values < 0.05 indicating statistical significance.

4. Results

One hundred and fifty-five patients 70 years or older with LSCLC or ESCLC were identified as the study population. Of the 155 patients, 84 had LSCLC and 71 had ESCLC. The median follow-up for surviving patients was 100 months (range 61–139 months). Table 2 lists relevant patient characteristics in patients receiving PCI versus no-PCI. For the entire patient population, 91 (59%) patients received PCI and 64 (41%) did not receive PCI. Of the 84 patients with LSCLC, 64 (76%) received PCI and 20 (24%) did not receive PCI. This was a higher proportion than was seen in the 71 patients with ESCLC, where only 27 (38%) received PCI and 44 (62%) did not receive PCI. Patients receiving PCI were more likely to have an ECOG performance status of 0 and were also less likely to have an ECOG performance status of 2 than patients who did not receive PCI ($p = 0.0235$). Patients with LSCLC were more likely to undergo PCI compared to ESCLC patients ($p < 0.0001$). In