ORIGINAL ARTICLE

Positive Interaction between Prophylactic Cranial Irradiation and Maintenance Sunitinib for Untreated Extensive-Stage Small Cell Lung Cancer Patients After Standard Chemotherapy: A Secondary Analysis of CALGB 30504 (ALLIANCE)

Joseph K. Salama, MD,[a,*] Lin Gu, MS,[b] Xiaofei Wang, PhD,[b] Herbert H. Pang, PhD,[b,c] Jeffrey A. Bogart, MD,[d] Jeffrey Crawford, MD,[e] Steven E. Schild, MD,[f] Everett E. Vokes, MD,[g] Neal E. Ready, MD, PhD[e]

[a]*Department of Radiation Oncology, Duke University, Durham, NC, USA*
[b]*Alliance Statistics and Data Center, Duke University, Durham, NC, USA*
[c]*School of Public Health, Li Ka Shing Faculty of Medicine, University of Hong Kong, Pok Fu Lam, Hong Kong SAR, People's Republic of China*
[d]*Department of Radiation Oncology, SUNY Upstate Medical Center, Syracuse, NY, USA*
[e]*Section of Medical Oncology, Department of Medicine, Duke University, Durham, NC, USA*
[f]*Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, USA*
[g]*Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago, IL, USA*

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ABSTRACT

Background: Prophylactic cranial irradiation (PCI) has become a standard option for patients with extensive-stage small cell lung cancer (ES-SCLC). The Cancer and Leukemia Group B 30504 trial was a randomized phase II study of the effect of sunitinib versus placebo in ES-SCLC patients responding to platinum-based systemic therapy. The study required preenrollment brain imaging. PCI was provided at the discretion of treating physicians. We performed a secondary analysis of the Cancer and Leukemia Group B trial to determine the impact of PCI on patients with ES-SCLC.

Methods: Fisher's exact test and the Wilcoxon rank-sum test were conducted to identify the differences between patients receiving PCI and patients not receiving PCI. Kaplan-Meier analyses described progression-free survival (PFS) and overall survival (OS) for patients in the PCI and non-PCI groups.

Results: A total of 85 patients received maintenance therapy (41 received placebo and 44 received sunitinib). Patient characteristics were balanced between the PCI and non-PCI groups. The patients receiving PCI plus sunitinib had a nonsignificant 2.7-month improvement in PFS (5.0 months versus 2.3 months, $p = 0.14$, hazard risk [HR] = 0.62, 95% confidence interval [CI]: 0.33–1.18) trending toward improved OS (8.9 months versus 5.4 months, $p = 0.053$, HR = 0.47, 95% CI: 0.22–1.03). PCI was associated with a trend toward improved median PFS (2.9 months versus 2.2 months, $p = 0.096$, HR = 0.69, 95% CI: 0.45–1.07) but not median OS (8.3 months in the PCI group versus 8.7 months in the non-PCI group, $p = 0.76$, HR = 1.07, 95% CI: 0.67–1.71). The patients receiving placebo had no improvement in PFS or OS with PCI.

Conclusions: Trends toward improved PFS and OS were seen in patients receiving PCI and sunitinib, thus supporting the need for further prospective research evaluating the integration of maintenance systemic therapy and PCI for patients with ES-SCLC. Improved outcomes for patients with ES-SCLC after induction chemotherapy may require PCI, thoracic radiotherapy, and maintenance systemic

*Corresponding author.

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Address for correspondence: Joseph K. Salama, MD, Duke University Medical Center, Box 3085, Durham, NC 27710. E-mail: joseph.salama@duke.edu

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therapy to achieve control of both intracranial and extracranial disease.

Keywords: Prophylactic cranial irradiation; Extensive-stage small cell lung cancer; Sunitinib; Maintenance chemotherapy; Survival

Introduction

Prophylactic cranial irradiation (PCI) is an established treatment for small cell lung cancer (SCLC). Although PCI was initially found to provide a survival benefit for patients with extensive-stage SCLC (ES-SCLC) who had a complete response (CR) after chemotherapy,[1] further studies found similar benefits in those who had any favorable response to chemotherapy in one trial and stable disease or better in a pooled analysis.[2,3] However, some oncologists have questioned the value of PCI in ES-SCLC because one of these studies did not require brain imaging before enrollment,[2] thus raising the possibility that the benefit may have been due to treatment of occult brain metastases. In addition, others have questioned these data because of the use of a wide range of radiation dose fractionation regimens and non–platinum-based systemic therapy. In fact, one randomized study that was undertaken specifically to address these concerns and included a standardized PCI dose, pre-PCI brain imaging, and platinum-based systemic therapy was closed early on account of its futility. In that study, patients with ES-SCLC who had been randomly assigned to the PCI arm showed a trend toward worse survival than did those patients who received no PCI (10.1 months versus 15.1 months, $p = 0.091$, hazard risk [HR] = 1.38, 95% confidence interval [CI]: 0.95–2.01).[4]

Cancer and Leukemia Group B (CALGB) 30504 was a double-blinded randomized phase II trial that compared maintenance sunitinib with placebo in untreated ES-SCLC patients, with disease control after up to six cycles of standard platinum-based chemotherapy. The CALGB 30504 protocol stated that patients having a partial response (PR) or CR after chemotherapy should be offered PCI, and almost half of the patients with responding tumors received PCI. Given these uncertainties as to the role of PCI for patients with ES-SCLC, we conducted a secondary analysis of survival outcomes in relation to PCI for the CALGB 30504 trial. We hypothesized that those patients in the CALGB 30504 trial who had received brain imaging before registration, standard platinum-based chemotherapy, and a standardized PCI regimen were more representative of patients with ES-SCLC given standard clinical care than were those in some clinical trials evaluating PCI in ES-SCLC. Furthermore, although PCI was recommended for all patients responding to systemic therapy in the CALGB 30504 trial, it was not administered to approximately half of patients achieving only a PR with chemotherapy for undocumented reasons. We therefore hypothesized that an analysis of the cohorts of patients who did and did not receive PCI in the CALGB30504 trial could contribute to a better understanding of the impact of PCI in ES-SCLC.

Methods

The methods of the CALGB 30504 trial have been published elsewhere.[5] Briefly, each participant signed an institutional review board–approved, protocol-specific informed consent document in accordance with federal and institutional guidelines. Four to six cycles of etoposide (100 mg/m^2 on days 1–3) and either carboplatin (area under the curve = 5) or cisplatin (80 mg/m^2 on day 1) were administered in 21-day cycles, followed by maintenance sunitinib versus placebo in patients with stable disease or a PR. The trial schema is shown in Figure 1. Before registration, patients were staged with contrast-enhanced computed tomography (CT) or magnetic resonance imaging of the brain, CT or magnetic resonance imaging of the chest (including the liver and adrenals), and either a bone scan or positron emission tomography scan (all within 42 days before registration). Patients achieving disease control after at least four but no more than six cycles of chemotherapy were randomly assigned (double-blind) to receive either placebo or sunitinib. Sunitinib was given at a dose of 150 mg orally on day 1 followed by 37.5 mg orally every day until progression. Patients were evaluated with CT of the chest (including the liver and adrenals) after every two cycles (every 6 weeks) while undergoing maintenance therapy. At time of progression, the patients who had been randomly assigned to receive placebo were allowed to cross over to sunitinib within 14 days. The primary and secondary objectives of the trial were to determine whether maintenance sunitinib would improve progression-free survival (PFS) and overall survival (OS), as was recently reported.[5]

PCI was recommended, but not required, for all patients with a PR or CR at the completion of four to six cycles of chemotherapy. The recommended dose was 25 Gy in ten 2.5-Gy fractions to a standard whole brain volume within 4 to 6 weeks after the last cycle of chemotherapy. Sunitinib was to be held for 2 days before, during, and 2 days after completion of PCI.

Statistical Methods

We performed this retrospective secondary analysis to investigate the effect of PCI in the prospectively