Single-Agent Versus Combination Chemotherapy in Patients with Advanced Non-small Cell Lung Cancer and a Performance Status of 2

Prognostic Factors and Treatment Selection Based on Two Large Randomized Clinical Trials

Rogerio Lilenbaum, MD, Victoria M. Villaflor, MD,† Corey Langer, MD,‡ Kenneth O'Byrne, MD,§ Mary O'Brien, MD,‖ Helen J. Ross, MD,¶ Mark Socinski, MD,# Fred B. Oldham, MD,** Larissa Sandilac, MD,** Jack W. Singer, MD,** and Philip Bonomi, MD††*

Purpose: Data from two randomized phase III trials were analyzed to evaluate prognostic factors and treatment selection in the first-line management of advanced non-small cell lung cancer patients with performance status (PS) 2.

Patients and Methods: Patients randomized to combination chemotherapy (carboplatin and paclitaxel) in one trial and single-agent therapy (gemcitabine or vinorelbine) in the second were included in these analyses. Both studies had identical eligibility criteria and were conducted simultaneously. Comparison of efficacy and safety was performed between the two cohorts. A regression analysis identified prognostic factors and subgroups of patients that may benefit from combination or single-agent therapy.

Results: Two hundred one patients were treated with combination and 190 with single-agent therapy. Objective responses were 37 and 15%, respectively. Median time to progression was 4.6 months in the combination arm and 3.5 months in the single-agent arm ($p < 0.001$). Median survival times were 8.0 and 6.6 months, and 1-year survival rates were 31 and 26%, respectively. Albumin <3.5 g, extrathoracic metastases, lactate dehydrogenase ≥ 200 IU, and 2 comorbid conditions predicted outcome. Patients with 0–2 risk factors had similar outcomes independent of treatment, whereas patients with 3–4 factors had a nonsignificant improvement in median survival with combination chemotherapy.

Conclusion: Our results show that PS2 non-small cell lung cancer patients are a heterogeneous group who have significantly different outcomes. Patients treated with first-line combination chemotherapy had a higher response and longer time to progression, whereas overall survival did not appear significantly different. A prognostic model may be helpful in selecting PS 2 patients for either treatment strategy.

Key Words: NSCLC, Performance status 2, Paclitaxel poliglumex, Gemcitabine, Vinorelbine, STELLAR, Prognostic model, Combination chemotherapy, Single-agent chemotherapy.

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Impaired performance status (PS) in non-small cell lung cancer (NSCLC) is associated with a poor prognosis and reduced tolerance to treatment. Although current guidelines support the use of systemic chemotherapy in patients with advanced NSCLC and PS 2, there is no consensus on specific treatment recommendations, particularly with respect to single-agent versus combination chemotherapy.[1,2]

Two large phase III randomized trials in advanced NSCLC patients with PS 2 compared paclitaxel poliglumex (PGT)/carboplatin to paclitaxel/carboplatin in one study (STELLAR 3), and single-agent PGT to either vinorelbine or gemcitabine in the second (STELLAR 4). These studies, whose results have been published elsewhere,[3,4] had identical eligibility criteria, were conducted simultaneously, and together represent the largest PS 2 patient population enrolled in randomized trials to date.

*Mount Sinai Cancer Center, Miami Beach, Florida; †Thomas Jefferson University Hospital, Philadelphia, Pennsylvania; ‡Fox Chase Cancer Center, Philadelphia, Pennsylvania; §St. James Hospital, Dublin, Ireland; ‖Royal Marsden Hospital, London, United Kingdom; ¶Mayo Clinic, Scottsdale, Arizona; #University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; **Cell Therapeutics, Inc., Seattle, Washington; and ††Rush-Presbyterian St. Luke's Medical Center, Chicago, Illinois.

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Address for correspondence: Rogerio Lilenbaum, MD, Mount Sinai Cancer Center, 4306 Alton Road, Miami Beach, FL 33140. E-mail: rlilenba@msmc.com

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We conducted a retrospective analysis of these data to evaluate the efficacy and safety of the two treatment strategies in the first-line management of advanced NSCLC patients with PS 2. A regression analysis was conducted to determine prognostic factors and identify patient subsets that might benefit from single-agent or combination chemotherapy.

PATIENTS AND METHODS

Eligibility Criteria and Treatment Plan

The study designs for STELLAR 3 and STELLAR 4 and the patient cohorts analyzed in this report are summarized in Figure 1. Briefly, STELLAR 3 was a phase III study comparing paclitaxel 225 mg/m^2 with PGT 210 mg/m^2, each in combination with carboplatin (area under the curve = 6), given every 3 weeks for up to 6 cycles. STELLAR 4 was a phase III comparison of single-agent PGT versus investigator's choice of gemcitabine or vinorelbine. At study initiation, the dose of PGT was 235 mg/m^2. As a result of toxicity in the first 96 patients, the dose of PGT was reduced to 175 mg/m^2 in all subsequent patients. PGT was administered on day 1 of each 21-day cycle for up to 6 cycles. Gemcitabine (1000 mg/m^2) was administered on days 1, 8, and 15 of each 28-day cycle, and vinorelbine (30 mg/m^2) was administered on days 1, 8, and 15 of each 21-day cycle. Both studies were conducted in North America, Western, and Eastern Europe between December 2002 and December 2003 (STELLAR 3), and December 2002 and June 2004 (STELLAR 4). There was no duplication of institutions. Both studies were approved by the institutional review boards and all patients provided written informed consent.

Eligible patients in both studies had confirmed NSCLC, an ECOG PS of 2, stage IV or stage IIIB disease not amenable to combined modality therapy, or recurrent disease previously treated with radiation and/or surgery. Prior systemic chemotherapy was not permitted. Patients with stable, treated brain metastases were eligible. Additional eligibility criteria included a baseline absolute neutrophil count ≥1500/μl; platelet count ≥100,000/μl; creatinine ≤1.5 times the upper limit of normal (ULN); bilirubin ≤ULN; transaminases ≤2.5 times ULN (≤5 times ULN in patients with hepatic metastases); and alkaline phosphatase ≤2.5 times ULN unless bone metastases were present.

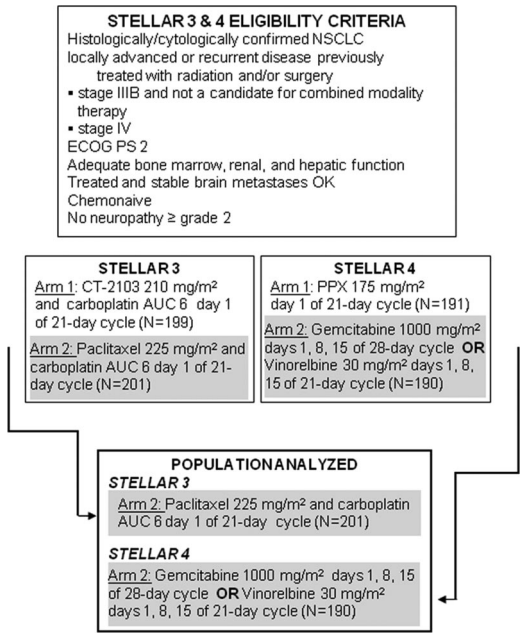

FIGURE 1. STELLAR 3 and 4 STUDY diagrams.

Statistical Considerations

The primary study end point in both STELLAR 3 and 4 was overall survival. Secondary objectives included response rate, assessed by response evaluation criteria in solid tumors (RECIST[5]), time to progression (TTP), disease control, safety, and quality of life. STELLAR 3 targeted accrual of 370 evaluable patients with 80% power and 0.05 type I error to show a 1.5-month improvement in median survival from a projected baseline of 4 to 5.5 months. In STELLAR 4, the original sample size was 370 patients. After the dose of PGT was reduced, the randomization ratio was adjusted to 2:1 and an additional 279 patients (185 randomized to PGT and 94 randomized to the comparator) were accrued, resulting in 80% power and 0.05 type I error to detect a 1.5-month median survival difference between the 2 treatment arms. The unstratified logrank test was used for the primary comparison of survival, which included all randomized patients. Toxicities were evaluated in all patients who received any amount of study drug using the National Cancer Institute Common Toxicity Criteria, version 2, and were compared using the Fisher's exact test. In both studies, disease-related symptoms were measured by the Functional Assessment of Cancer Therapy-Lung Cancer Scale.

This analysis compares efficacy and safety outcomes for patients treated in the control arms of both studies ("combination chemotherapy": carboplatin/paclitaxel and "single-agent therapy": gemcitabine or vinorelbine). Comparison of response and toxicity rates between patients treated with combination chemotherapy versus single agent therapy was made using the Fisher's exact test. Based on the fact that no statistically significant difference in outcomes was observed between the control and the experimental arms in both trials, the regression analysis was performed in the entire population of STELLAR 3 and 4 to increase the power. The Cox proportional hazards model was used for identification of prognostic factors associated with survival and Kaplan-Meier estimates were used to assess medians and percentiles.

RESULTS

Baseline Characteristics

There were 201 patients in the combination cohort and 190 patients in the single-agent cohort. In the latter, 32 patients received vinorelbine and 155 received gemcitabine. Patient demographics are shown in Table 1. The majority of patients were accrued from Eastern European sites. Median age was 63 and 64, respectively, with approximately 23% of patients aged 70 or older in both groups. Approxi-