Multitrial Evaluation of Progression-Free Survival as a Surrogate End Point for Overall Survival in First-Line Extensive-Stage Small-Cell Lung Cancer

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Introduction: We previously reported that progression-free survival (PFS) may be a candidate surrogate end point for overall survival (OS) in first-line extensive-stage small-cell lung cancer (ES-SCLC) using data from three randomized trials (Foster, Cancer 2011). In this validation study (N0424-Alliance), we assessed the patient-level and trial-level surrogacy of PFS using data from seven new first-line phase II/III ES-SCLC trials and across all 10 trials as well (seven new, three previous).

Methods: Individual patient data were utilized across the seven new trials (2259 patients) and all 10 trials (2855 patients). Patient-level surrogacy (Kendall's τ) was assessed using the Clayton copula bivariate survival model. Trial-level surrogacy was assessed through association of the log hazard ratios on OS and PFS across trials, including weighted (by trial size) least squares regression (WLS R^2) of Cox model effects and correlation of the copula effects (copula R^2). The minimum effect on the surrogate (MES) needed to detect a nonzero treatment effect on OS was also calculated.

Results: The median OS and PFS across all 10 trials were 9.8 and 5.9 months, respectively. PFS showed strong surrogacy within the 7 new trials (copula $R^2 = 0.90$ [standard error = 0.27], WLS $R^2 = 0.83$ [95% confidence interval: 0.43, 0.95]; MES = 0.67, and Kendall's $\tau = 0.58$) and across all 10 trials (copula $R^2 = 0.81$ [standard errors = 0.25], WLS $R^2 = 0.77$ [95% confidence interval: 0.47–0.91], MES = 0.70, and Kendall's $\tau = 0.57$).

Conclusions: PFS demonstrated strong surrogacy for OS in first-line ES-SCLC based on this external validation study of individual patient data. PFS is a good alternative end point to OS and should be considered when resource constraints (time or patient) might make it useful or desirable in place of OS. Additional analyses are needed to assess its appropriateness for targeted agents in this disease setting.

Key Words: Extensive-stage small-cell lung cancer, Surrogate endpoints, Pooled analysis, Progression-free survival, Overall survival.

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Lung cancer is expected to cause 159,260 deaths within the United States in 2014.[1] Approximately 15% of lung cancer patients have small-cell lung cancer (SCLC),[2] and approximately 70% of patients with SCLC have extensive-stage disease (ES-SCLC).[2] For patients with ES-SCLC, the current standard treatment in the first-line setting is etoposide and platinum,[3–6] which generally yields a median overall survival (OS) in the range of 8–12 months. Unfortunately, few dramatic improvements in ES-SCLC therapy have been made in the past 20 years,[7] leading to a situation where a shorter term, surrogate end point could make testing future therapies more efficient.

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OS remains the most relevant clinical end point within oncology clinical trials, including ES-SCLC. Because the median OS for ES-SCLC patients is relatively short, one may wonder why it would be important to find a valid surrogate end point for OS in this disease. The reasons that a valid surrogate end point may still be important in this setting include the fact that a valid surrogate would allow a shorter follow-up time requirement for clinical trials of new agents, and the potential that effective subsequent therapies, such as topotecan,[8] may make it difficult to assess the true treatment effect of an agent in the first-line setting. Moreover, many phase II trials in SCLC continue to use response rate as the primary end point, with no supporting evidence of its association to true clinical benefit.[9] A surrogate end point is one that can substitute for a true clinical end point and can predict patient outcome sooner than with the true end point.[10,11] To demonstrate that an end point is a valid surrogate, it must meet two criteria. First, the surrogate end point must be associated with the true clinical end point (patient-level surrogacy), and second, the treatment effects on the surrogate end point must be strongly associated with the treatment effects on the true end point (trial-level surrogacy).[10,11] If both of these criteria are met, it can be argued that the surrogate end point is valid and can be used in place of the true end point.

A PubMed literature search for trials reported over a 10-year period (2005–2014) in first-line ES-SCLC in the phase II setting showed that only 8 of the 46 published trials used progression-free survival (PFS) as the primary end point, with OS being used even less often (7 of 46 trials). Nearly all phase II studies over this period used response as the primary end point (30 of 46). Even in the randomized Phase II setting, response was used more often than PFS, where 7 of the 10 randomized Phase II studies used response as the primary end point and only 2 used PFS. We previously reported that PFS may be a candidate surrogate end point for OS in first-line ES-SCLC using data from three randomized North Central Cancer Treatment Group (NCCTG) trials (2, phase III; 1, phase II).[9] This prior study also demonstrated that PFS is a better predictor of OS than tumor response;[9] however, PFS is still not routinely used as the primary end point in the phase II setting in ES-SCLC.

PFS is defined as the time from study registration or randomization to the first of either disease progression or death from any cause. Issues with PFS as an end point are well documented and discussed elsewhere.[12–18] Despite the many issues with PFS, it is considered a possible surrogate end point for OS, as it is unaffected by subsequent therapies and could shorten the time to drug approval. Given preliminary promising evidence of PFS as a candidate surrogate end point for OS, we sought to formally assess the patient-level and trial-level surrogacy of PFS using data from seven additional first-line randomized phase II/III trials (2259 patients). For this analysis, individual patient data from the seven new trials and 10 total trials (including the three previous trials) were utilized, which included eight phase III and two phase II studies. These 10 trials (2855 patients) consisted of a series of published first-line randomized phase II/III studies conducted by the NCI-funded cooperative groups or JCOG since 1982, which represents the largest individual patient data analysis in this disease setting that includes multicenter cooperative group trials conducted within the United States, Canada, and Japan.

MATERIALS AND METHODS

Data and Trial Characteristics

Individual patient data were utilized from the seven new non-NCCTG trials (2259 patients) and all 10 randomized ES-SCLC first-line therapy trials that accrued 2855 patients between 1982 and 2007 (Table 1).

This included eight phase III studies and two phase II studies. The radiographic scanning interval was similar across all studies, where it was generally from 3 to 6 weeks during treatment. One trial had four treatment arms, thus 12 total two-arm comparisons were made. OS was the primary end point in all phase III trials. For the phase II studies, the primary end point was 1-year OS rate (CALGB 30103) or response rate (NCCTG 932053), with none powered for OS (i.e., time-to-death). The randomized phase II studies were included because of the low number of available randomized trials in this disease setting. Three phase III trials and one randomized phase II trial showed a significant OS benefit for the experimental treatment versus the control treatment (National Cancer Institute of Canada Clinical Trials Group [NCIC CTG] BR4, JCOG 9511, NCCTG 862051, NCCTG 932053; Table 2). In addition, one trial demonstrated significantly worse OS for the experimental treatment versus the control treatment (CALGB 30103; Table 2).

Institutional Review Boards at the study sites had previously approved these trials, and all participants provided written informed consent. This analysis was conducted under an IRB approved protocol (N0424-Alliance). See Table 1 for a detailed listing of the individual trial characteristics, where the three NCCTG trials were reported previously.[9]

Statistical Methods

This study assessed the association between PFS and OS at both the patient-level and trial-level. First, we assessed the patient-level and trial-level surrogacy of PFS using data from seven new first-line phase II/III ES-SCLC trials to externally validate our previous findings. Subsequently, the patient-level and trial-level surrogacy was also assessed across all 10 trials (including the data from the three previously reported trials). PFS was defined as the time from randomization to the first of either disease progression or death from any cause, where the progression status was typically based on preresponse evaluation criteria in solid tumors (pre-RECIST; 8 of 10 trials). Because we did not have the raw tumor measurement data across all studies, we were unable to convert the progression status into one specific criterion (RECIST vs. pre-RECIST). For this analysis, therefore, we used the progression status information that was collected and reported for each trial. OS was defined as the time from randomization to death from any cause.

Patient-level surrogacy was assessed using a bivariate survival model constructed from a Clayton copula with Weibull marginal distributions, as developed by Burzykowski et al.[10] and updated by Renfro et al.[29] Specifically, the copula association parameter (assumed equal across trials) was transformed onto the scale of Kendall's $\tau \in [-1, 1]$, where a value of τ equal to 1 would indicate a perfect positive association between OS