Relevance of Platinum-Sensitivity Status in Relapsed/Refractory Extensive-Stage Small-Cell Lung Cancer in the Modern Era

A Patient-Level Analysis of Southwest Oncology Group Trials

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Background: Extensive-stage small-cell lung cancer (SCLC) patients who progress after platinum-based chemotherapy are traditionally categorized as platinum sensitive (progression ≥ 90 days from last platinum dose) or refractory (progression < 90 days), a practice arising from seminal observations of worse survival in refractory patients. Subsequent trials accounted for platinum sensitivity, resulting in higher sample sizes and increased resource use.

Methods: To assess whether platinum-sensitivity status remains associated with outcomes, patient-level data from recent Southwest Oncology Group trials in second- and/or third-line extensive-stage SCLC were pooled. Hazard ratios (HRs) for progression-free survival (PFS) and overall survival (OS) accounting for platinum sensitivity were calculated using unadjusted and adjusted Cox Proportional Hazard models. Recursive partitioning was performed to define prognostic risk groups.

Results: Of 329 patients, 151 were platinum sensitive and 178 refractory. HRs from unadjusted Cox PFS and OS models for refractory versus sensitive disease were 1.0 (95% confidence interval, 0.81–1.25; $p = 0.98$) and 1.24 (0.99–1.57; $p = 0.06$), respectively. Adjusted Cox models showed that only elevated serum lactate dehydrogenase (HR, 2.04; $p < 0.001$), males (HR, 1.36; $p = 0.04$), performance status of 1 (HR, 1.25; $p = 0.02$), and weight loss greater than or equal to 5% (1.53, $p = 0.01$) were independently associated with OS. Platinum-sensitivity status was not associated with PFS (HR, 1.11; $p = 0.49$) or OS (HR, 1.25; $p = 0.14$), except in a model that excluded 36 patients who received more than one prior chemotherapy regimen (HR, 1.34; $p = 0.049$). Prognostic groups with differential OS outcomes (high, intermediate, and poor risk) were identified.

Conclusions: Platinum-sensitivity status may no longer be strongly associated with PFS or OS in at least one multivariate model. Validation of prognostic risk groups identified here is warranted. These data have critical implications in the design of future SCLC trials.

Key Words: Small-cell lung cancer, Platinum sensitive, Platinum refractory, Clinical trials, Treatment, Southwest Oncology Group.

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Disease progression after initial platinum-based chemotherapy is almost universal in patients with extensive-stage small-cell lung cancer (SCLC).[1] At the time of progression, patients have traditionally been categorized as either platinum sensitive (defined as progression > 90 days from last platinum dose) or platinum refractory (progression < 90 days from last platinum dose). Patients who progress while receiving platinum-based therapy are sometimes labeled as "platinum resistant"; however, many clinicians likewise define these patients as "platinum refractory" as well.

The practice of categorizing patients according to platinum-sensitivity status arose from observations in a phase II trial of the investigational cytotoxic agent teniposide.[2] In this trial that accrued 50 previously-treated SCLC patients, longer time from prior chemotherapy discontinuation (i.e., >2.6 mo) and response to prior chemotherapy were found to be associated with response to subsequent teniposide.

Since those seminal observations, subsequent efficacy trials in SCLC began accounting for platinum-sensitivity status. In many cases, this resulted in more complex studies, higher sample sizes and increased resource use. Some studies opted to solely focus on the platinum-sensitive group, excluding those with refractory disease.[3,4] In Southwest Oncology Group (SWOG), trials in previously treated SCLC since 2000 have mandated independent accrual to platinum-sensitive and platinum-refractory strata to account for the possibility of differential outcomes to investigational therapies between these

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groups. However, recent trials (both SWOG and non-SWOG) have not shown divergent outcomes related to platinum-sensitivity status.[5–9]

In the past decade, SWOG has conducted three phase II trials of investigational regimens in platinum-treated SCLC (S0802, S0435, and S0327); these trials are summarized in Table 1.[5–7] In these studies, progression-free survival (PFS) and overall survival (OS) were generally comparable between platinum-sensitive and platinum-refractory strata across all trials, except for S0802 where modest advantage for PFS and OS in the aflibercept-containing arm was demonstrated. Similarly, the final results of a recent non-SWOG phase II trial of temozolomide in platinum-treated SCLC also showed no clear differences in outcomes dependent on platinum-sensitivity status.[10] We therefore sought to evaluate the association between platinum-sensitivity status and SCLC patient outcome in the modern era using the pooled SWOG database.

METHODS

Updated patient-level data from S0802, S0435, and S0327 were pooled. S0802 randomized patients to either topotecan alone or topotecan plus the angiogenesis inhibitor aflibercept (vascular endothelial growth factor [VEGF]-Trap). S0435 was a single arm trial of the vascular endothelial growth factor tyrosine kinase inhibitor (VEGFR-TKI) sorafenib. S0327 was a single arm trial of the proteasome inhibitor PS-341 (bortezomib). Each of the trials had consistent eligibility criteria and collected the same baseline demographic variables. The primary endpoint for S0802 was 3-month PFS, whereas the primary endpoint for S0435 and S0327 was response rate. All staging definitions used by SWOG for these trials preceded the 7th edition of the tumor, node, metastasis staging system. All studies were reviewed and approved by Institutional Review Boards and all patients gave written informed consent.

Multivariate Cox regression models were fit to assess the relationship between baseline characteristics and PFS and OS. PFS and OS estimates were calculated using the method of Kaplan–Meier. Confidence intervals for the median were constructed using the method of Brookmeyer–Crowley. All p values were two-sided. To investigate a predictive model for OS, recursive partitioning was performed using the likelihood tree model of LeBlanc and Crowley.[11] The minimum node size was set at 20.

OS was defined as the duration from the date of enrollment to the date of death due to any cause. Patients last known to be alive were censored at the date of last contact. PFS was defined as the duration from the date of enrollment to the date of first documentation of disease progression, as defined by Response Evaluation Criteria in Solid Tumors, symptomatic deterioration without documented disease progression, or death due to any cause. Patients last known to be alive and without evidence of disease progression or symptomatic deterioration were censored at the date of last contact. Disease assessments were performed every 6 weeks in all three protocols.

RESULTS

Three hundred twenty-nine patients constituted the pooled study population. Patient characteristics stratified by platinum-sensitivity status are summarized in Table 2. Of 329 patients, 151 were categorized as platinum sensitive and 178 were platinum refractory. Median age was 63 years. Males comprised 52% of the group while those with performance status one constituted 67%. There were 89 patients (28%) with clinically significant weight loss of greater than or equal to 5% within the preceding 3 months. Elevated lactate dehydrogenase (LDH) levels were seen in 43%.

Crude unadjusted analysis of PFS and OS stratified by platinum-sensitivity status are summarized in Figure 1. The hazard ratio (HR) for PFS (refractory/sensitive) was 1.0 (95% confidence interval [CI], 0.81–1.25), with a p value of 0.98. The HR for OS (refractory/sensitive) was 1.24 (95% CI, 0.99–1.57), with a p value of 0.06.

Multivariate analysis of baseline clinical variables and PFS (Table 3) showed that only elevated LDH (HR, 1.83; $p < 0.0001$) and trial assignment to S0802 (HR, 1.82; $p = 0.001$) were independently prognostic for PFS. In contrast, platinum-sensitivity status was not associated with PFS. Multivariate analysis for OS (Table 4) showed that platinum-sensitivity status was also not associated with OS (HR, 1.25; $p = 0.14$). Instead, elevated LDH (HR, 2.04; $p < 0.0001$), weight loss (HR, 1.53; $p = 0.01$), performance status of one (HR, 1.43; $p = 0.02$), and male sex (HR, 1.36; $p = 0.04$) were found to be the only clinical variables associated with worse OS. In a subsequent analysis, 14 patients (six from S0435 and eight from S0802) had their prior chemotherapy status changed from two or more to exactly one. An additional three patients (two on S0435 and one on S0802) who had missing data were assumed to have received exactly one prior chemotherapy regimen. (The eligibility criteria stated that these patients must have received exactly one prior regimen when all 17 of these patients were enrolled.) When these 17 patients who had exactly one prior chemotherapy were reclassified, multivariate analysis subsequently showed that prior chemotherapy was significantly associated with improved OS (HR, 0.29; $p = 0.03$). Sex, LDH, weight loss, and performance

TABLE 1. Recent Phase II SWOG Trials in Extensive-Stage Small-Cell Lung Cancer

SWOG Study	Regimen	No. of Patients	Performance Status Allowed	No. of Prior Regimens Allowed
S0327	Bortezomib	57	0–1	≥1
S0435	Sorafenib	83	0–1	1[a]
S0802	Topotecan ± aflibercept	189	0–1	1

[a]S0435 was amended to restrict the study population to patients having received only one prior regimen after it had enrolled 22 patients.
SWOG, Southwest Oncology Group.

