



Thriving where others have faltered—a critical appraisal of the role of patient factors versus treatment effect in JCOG0605 trial in relapsed small cell lung cancer

Nikita T. Patel¹, Taofeek K. Owonikoko^{1,2}

¹Department of Hematology & Medical Oncology, ²Thoracic Oncology Program, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA 30322, USA

Correspondence to: Taofeek K. Owonikoko, MD, PhD. Associate Professor, Co-Director, Department of Hematology & Medical Oncology, Thoracic Oncology Program, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA 30322, USA. Email: towonik@emory.edu.

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Small cell lung cancer (SCLC) makes up approximately 13–15% of all lung cancer cases (1). Despite initial response to treatment, a large majority of patients with extensive stage SCLC relapse within 6 months (2). Improved outcome for SCLC patients remains stunted in major part because of lack of effective therapies for progressive disease following frontline therapy. Topotecan is the only salvage therapy with worldwide approval but its efficacy is quite modest and may be ineffective in patients with platinum insensitive disease (3–5). Contemporary comparative phase III studies of cytotoxic agents such as cabazitaxel and amrubicin against topotecan for relapsed SCLC have been negative especially in Western patient populations (6,7). It is therefore intriguing and interesting to observe that the randomized phase III JCOG0605 trial recently reported by Goto *et al.* showed an impressive benefit of the combination of cisplatin, etoposide and irinotecan, which significantly outperformed topotecan as second line therapy for patients with sensitive relapsed SCLC (8).

The study compared topotecan as standard therapy to the investigational regimen of cisplatin, etoposide and irinotecan in an open label, multicenter randomized trial that enrolled 180 patients with 90 patients per arm. Treatment was administered along with growth factor support as five 2-week cycles of combination chemotherapy (cisplatin 25 mg/m² on days 1 and 8, etoposide 60 mg/m² on days 1–3 and irinotecan 90 mg/m² on day 8) versus single agent topotecan (1.0 mg/m² on day 1–5 every 3 weeks) for four cycles. An impressive median overall survival of

18.2 months (95% CI, 15.7–20.6) versus 12.5 months (95% CI, 10.8–14.9) with more than 30% reduction in the risk of death (stratified HR, 0.67; 90% CI, 0.51–0.88; P=0.0079) was recorded in favor of the experimental arm. This is an unprecedented result in this disease especially in the relapsed setting. An astounding result like this therefore warrants a critical appraisal of various aspects of the study design, the selection of the experimental and comparator treatments, as well as the patient population for proper contextualization of the data. Several prognostic factors are associated with improved outcome in SCLC including, performance status, gender, burden of disease and response to platinum-based frontline therapy (9). The JCOG0605 study was designed to compare efficacy of two regimens in patients who progressed following frontline therapy with restriction to patients with sensitive relapse. While topotecan is an acceptable regimen for this population, retreatment with platinum doublet is also an established and perhaps preferable option for those with treatment free interval of more than 180 days, as observed in a significant proportion of patients enrolled on the JCOG0605 study (10,11). Nonetheless, the fact that 84% of patients on topotecan arm subsequently received additional therapies including doublet chemotherapy would suggest that failure to employ platinum doublet, as the comparator could not explain the impressive overall survival benefit of the experimental regimen over topotecan in this study.

Previous studies that tested empiric combination of triplet chemotherapy failed to improve outcome in part

because of increased toxicity but also due to lack of a valid biological premise for the combination of agents to have improved efficacy (12). However, preclinical studies showed that resistance to topoisomerase enzyme 1 (TOP-1) inhibitors might be secondary to down regulation of TOP-1 targets, which induces an up-regulation of TOP-2 targets. Conversely, TOP-2 inhibition down regulates TOP-2 targets and up-regulates TOP-1 (13,14). This preclinical data provides a biological premise for the expectation of improved efficacy with the triplet regimen of cisplatin, etoposide and irinotecan and could also explain the improved survival recorded in the JCOG0605 study. However, a similar approach tested by US investigators in ECOG 5501, a randomized phase II trial that compared the effectiveness of cisplatin, etoposide and topotecan combination (TPE) to irinotecan, cisplatin, etoposide and irinotecan (PIE) as first line therapy in extensive stage SCLC, failed to show a survival benefit (15). Similar to the JCOG0605 study, there was significant toxicity with grade ≥ 3 treatment-related adverse events in approximately 70% of patients and only 55% of all enrolled patients completed six cycles of treatment as planned. The overall response rates on both arms of the E5501 study were much more modest at 70% for the PET regimen and 58% for the PIE arm in a previously untreated patient population. Moreover, the median overall survival of 11.9 and 11.0 months for both arms was no better than would be expected for platinum doublet chemotherapy and the two regimens were therefore deemed uninteresting to warrant a definitive phase III study. We previously showed in a meta-analysis of results of clinical studies in relapsed SCLC that objective response rate to salvage chemotherapy in sensitive relapse SCLC patients is double the rate for resistant disease (16). However, 80% response rate for the triplet chemotherapy regimen in the JCOG0605 study in the relapsed setting is quite unusual even for platinum sensitive disease. Moreover, the modest efficacy of a similar regimen in the E5501 study and the fact that the response rate for the topotecan arm was only 27%, which is comparable to historical data, makes one wonder about other factors beyond the chemotherapy that could have contributed to this outcome.

The study population is another factor to consider as possible contributor to the survival benefit of the triplet chemotherapy in the JCOG0605 study. Ethnic based differences in the effectiveness and adverse event profiles of topoisomerase inhibitors are well recognized. It is also well demonstrated that irinotecan may be more effective in Japanese population in part due to pharmacogenomic differences but the magnitude of benefit of irinotecan in the frontline or post frontline setting for Japanese patients quite modest and not sufficient to explain the survival benefit observed in the

JCOG0605 study (17-20). Finally, the study population was defined as those with sensitive relapsed SCLC, which on face value implies that most of these patients were extensive stage disease patients who have progressed and need second line treatment. However, a quarter of the patients were originally diagnosed with limited stage disease and more than 40% of the patients received radiation along with chemotherapy for the frontline therapy. It is unclear how many of these patients progressed outside the original site of disease. This study population should therefore not be taken as fully representative of the typical second line extensive stage SCLC patient population. Perhaps the enrichment for patients with limited stage disease and those with low volume extensive stage disease contributed to the improved survival recorded in this study. Additionally, since this population is already preselected for platinum sensitivity, one could speculate that retreatment with an intensified platinum-based regimen really amplified the efficacy out of proportion to what would be expected in an unselected patient population as was the case with the E5501 study. Regardless of the reason for this impressive survival benefit, this approach highlights a potential opportunity to exploit for improved outcome for SCLC patients. It is conceivable that a similar strategy to intensify platinum doublet chemotherapy in platinum sensitive relapse using biologically rational agents such as PARP inhibitors and mTOR inhibitors without overlapping toxicity could lead to comparative or even greater survival benefit and without additive toxicity.

In conclusion, the JCOG0605 trial demonstrated a significant advantage to a three-drug chemotherapy combination and identified another salvage therapy option for sensitive relapse SCLC. Real world application of this regimen will be limited by the significant hematologic toxicity and careful patient selection focusing on those with small volume disease who achieved objective response to frontline platinum doublet chemotherapy. Moreover, whether this regimen is applicable to Western population of patients would require additional investigation given the known differences in topoisomerase inhibitor efficacy and toxicity between Japanese and non-Japanese patients of North America and Europe.

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Footnote

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