



Cisplatin, etoposide, and irinotecan for relapsed small-cell lung cancer

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Comment on: Goto K, Ohe Y, Shibata T, *et al.* Combined chemotherapy with cisplatin, etoposide, and irinotecan versus topotecan alone as second-line treatment for patients with sensitive relapsed small-cell lung cancer (JCOG0605): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2016;17:1147-57.

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Small-cell lung cancer (SCLC) is one of the most chemosensitive solid tumors. Unfortunately, a majority of patients will experience relapse of their disease within 1 year of completing treatment. Median survival for patients with relapsed disease is dismal at about 5–6 months even with best available therapy. Good performance status and sensitivity to first-line chemotherapy are significant prognostic factors of survival in patients treated for relapsed SCLC (1). Therapy options for relapsed SCLC remain limited, due to poor efficacy of most chemotherapy regimens and the poor performance status of many of these patients at relapse. Currently, topotecan is the only FDA-approved agent for the treatment of relapsed SCLC based on a phase III trial that demonstrated improvement in survival and quality of life (QOL) compared to best supportive care (2).

Goto *et al.*, on behalf of the Japan Clinical Oncology Group, recently published a multi-center phase III trial evaluating combination chemotherapy with cisplatin, etoposide, and irinotecan versus single-agent topotecan for the treatment of patients with relapsed SCLC (JCOG0605). Patients with sensitive relapsed SCLC (recurrence or progression of disease at least 90 days after completion of first-line treatment) were randomized in a 1:1 fashion to receive either combination chemotherapy or single-agent topotecan (3). The combination therapy group had improved overall survival (18.2 *vs.* 12.5 months; $P=0.0079$) and progression-free survival (5.7 *vs.* 3.6 months; $P<0.0001$). The proportion of patients who had disease response was also higher in the combination group (84% *vs.* 27%; risk

ratio 0.32; $P<0.0001$). Based on the results of this study, the authors suggested that combination chemotherapy with cisplatin, etoposide, and irinotecan could be considered as the standard second-line treatment for sensitive relapsed SCLC.

While the authors should be commended for the randomized nature of their trial and the relevance of the question they addressed, there are several aspects of the patient selection and outcomes of this study that raises concerns regarding the general applicability of their results.

Greater than 70% of patients in both groups (72% in the topotecan group and 78% in the combination group) had extensive-stage SCLC at entry into the study. The goal of chemotherapy in this setting is palliative and therefore, QOL becomes an even more important consideration. The combination regimen that Goto *et al.* utilized in their study was very intensive—cisplatin given on days 1 and 8, etoposide on days 1–3, and irinotecan on day 8 of a 21 day cycle. Given the myelosuppressive nature of this regimen, G-CSF support was given daily starting on day 9. QOL was not formally assessed. However, the toxicity of this combination regimen was significant; febrile neutropenia occurred in 31% of patients in the combination group compared to only 7% in the single-agent topotecan group, and more patients experienced a serious adverse event (10% *vs.* 4%). In addition, 50% of patients in the combination group required a dose reduction and 84% had a dose delay. Overall, the toxicity profile of cisplatin, etoposide, and irinotecan raises significant concerns about the tolerability of this regimen.

The authors did not collect information on the number of patients screened, number of patients who were not eligible, and number of patients who declined participation in the study. This introduces the possibility of enrollment bias, which is supported by the low overall enrollment rate of < two patients per institution per year.

Imbalances in baseline characteristics between the two groups may have skewed results to favor survival in the combination group. In general, over 90% of patients in each group had an ECOG performance status of 0–1, which does not reflect the typical patient with relapsed SCLC. However, 58% of patients in the combination group had an ECOG performance status of 0 compared to 44% of patients in the topotecan group. The impressive performance status of these patients is likely a significant contributor to the relatively good survival noted in both arms of this study. In fact, the results of a study by Sundström *et al.* showed that performance status at recurrence was the only independent predictor of survival in patients with relapsed SCLC (4). Goto *et al.* also did not report the number of patients with extensive stage disease in each group nor the proportion that received prophylactic cranial irradiation, which has also been shown to improve overall survival (5).

The median time to relapse in the combination group was substantially greater than in the topotecan group (181 *vs.* 148 days, respectively). Increased time to recurrence is also a positive prognostic factor for survival (1). In current practice, the time to relapse in SCLC also influences the chemotherapy that is recommended. Per NCCN guidelines, a platinum and etoposide doublet is the recommended first-line therapy. If relapse occurs more than 6 months after completion of first-line therapy, reuse of the initial regimen should be considered in patients with eligible performance status (6). The interquartile range for time to relapse in the topotecan group was 113–228 days (7.8 months) with a range of 92–2,318 days (6.4 years). This, in addition to their overall excellent performance status, suggests that a subset of the patients randomized to the topotecan group were eligible to receive a platinum-etoposide doublet and were therefore undertreated. In their study, Goto *et al.* administered topotecan at 1.0 mg/m² IV on days 1–5 of a 21 day cycle, which is lower than 1.5 mg/m² that is the approved dose in the United States. Huber *et al.* found that that a topotecan dose of 1.25 mg/m² is equally efficacious to the 1.5 mg/m² dose (7) and a phase II Japanese study showed continued efficacy of topotecan at 1.0 mg/m² (8). Therefore, the lower topotecan dose likely did not contribute to the

improved overall survival of the combination chemotherapy group.

Unfortunately, efficacious treatment options for relapsed SCLC remain limited. Although the results of JCOG0605 are provocative, they cannot be generalized to the average patient with relapsed SCLC. Therefore, while a select few patients who are very fit could be considered for combination chemotherapy with cisplatin, etoposide, and irinotecan, the regimen will likely not be tolerated by most and should not be considered as standard second-line treatment.

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Footnote

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