

## Chemotherapy for small-cell lung cancer

For more than two decades, etoposide plus cisplatin has been the standard chemotherapy regimen for patients with small-cell lung cancer (SCLC). The present standard treatment for limited-stage SCLC, etoposide plus cisplatin and early, concurrent thoracic radiotherapy followed by prophylactic cranial irradiation, was established by the INT0096 trial<sup>1</sup> in 1999. The paucity of progress in chemotherapy for SCLC has not been due to lack of effort; many novel strategies have been assessed in clinical trials without evidence of reproducible benefit.

The most extensively studied alternative regimen has been irinotecan plus cisplatin. Interest in this regimen was heightened by a randomised trial<sup>2</sup> from the Japan Clinical Oncology Group (JCOG) that reported a significant improvement in survival for irinotecan plus cisplatin compared with etoposide plus cisplatin in patients with extensive-stage SCLC. However, this enthusiasm dimmed upon publication of randomised trials that failed to confirm the superiority of irinotecan plus cisplatin compared with etoposide plus cisplatin in non-Japanese patients with extensive-stage SCLC.<sup>3,4</sup> Since then, the question of irinotecan versus etoposide has been kept alive by two meta-analyses reporting improved overall survival with irinotecan.<sup>5,6</sup>

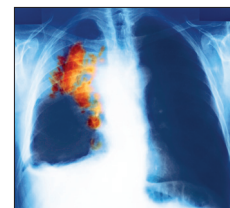
In *The Lancet Oncology*, the JCOG investigators, led by Kaoru Kubota and colleagues,<sup>7</sup> report the results of a phase 3, randomised trial of irinotecan plus cisplatin versus etoposide plus cisplatin consolidation therapy after induction with etoposide plus cisplatin and accelerated, hyperfractionated thoracic radiation therapy (AHTRT) in 281 Japanese patients with limited-stage SCLC. By contrast with the previous JCOG study comparing these regimens in extensive-stage SCLC,<sup>2</sup> the present study failed to show a significant difference in overall survival between irinotecan plus cisplatin and etoposide plus cisplatin (median overall survival 2.8 years [95% CI 2.4–3.6] vs 3.2 years [2.4–4.1]; hazard ratio 1.09 [95% CI 0.80–1.46], one-sided stratified  $p=0.70$ ).

The use of irinotecan plus cisplatin in locally advanced lung cancer was previously explored in phase 1 and 2 trials. To take advantage of the radiosensitising properties of irinotecan, initial studies attempted to administer irinotecan plus cisplatin concurrently with thoracic radiotherapy. However, because of safety concerns with this approach, the strategy shifted to

the assessment of irinotecan plus cisplatin as induction or consolidation therapy before or after etoposide plus cisplatin and thoracic radiotherapy. Two phase 2 studies<sup>8,9</sup> reported reasonable efficacy outcomes using the same regimen as studied in the present JCOG trial, one cycle of etoposide plus cisplatin and concurrent AHTRT followed by three cycles of irinotecan plus cisplatin. Importantly, overall survival in these trials did not differ substantially from that obtained with four cycles of etoposide plus cisplatin plus AHTRT in INT0096, the most relevant historical control (median overall survival was 20 months<sup>8</sup> and 23 months<sup>9</sup> vs 23 months;<sup>1</sup> at 2 years, there were 41%<sup>8</sup> and 49%<sup>9</sup> vs 47%<sup>1</sup> of patients alive in the studies). In retrospect, these findings presaged the negative results of the present JCOG trial and suggest that clinical researchers need to raise the standard of what are deemed promising phase 2 outcomes to better justify large, phase 3 trials. In view of the previous phase 2 results, the best outcome to be hoped for from the present trial would have been a marginal improvement in overall survival of questionable clinical significance.

Why did this study fail to show any improvement in outcome with irinotecan plus cisplatin? The most likely explanation is that, despite the previous JCOG trial and recent meta-analyses, irinotecan plus cisplatin is truly no better than etoposide plus cisplatin. The planned drug regimens in the present study were identical to those in the JCOG trial in extensive-stage SCLC and, aside from the difference in stage, the populations were much the same, with both trials<sup>2,7</sup> enrolling patients aged up to 70 years. The present trial<sup>7</sup> supports the clinical impression that irinotecan plus cisplatin is more toxic than etoposide plus cisplatin, reporting lower deliverable dose intensity and a greater percentage of patients terminating treatment because of toxicity with irinotecan plus cisplatin. Importantly, the previous JCOG trial<sup>2</sup> in extensive-stage SCLC was terminated early because of positive findings from an interim analysis, resulting in a small sample size in which serendipitously favourable outcomes in a few patients might have led to a misleading conclusion.

The present JCOG trial was started 11 years ago, in 2002. Is a trial comparing two cytotoxic chemotherapy agents still relevant in the age of personalised,



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genomic-based therapy? Are topoisomerase I and II still the best therapeutic targets? Unfortunately, because cytotoxic chemotherapy remains an integral part of the standard treatment for SCLC, the choice of regimen is still a clinically relevant question. Many molecular targets have been identified in SCLC, but thus far, clinical trials of therapeutic strategies directed against these targets have not yielded promising results. Recently, SCLC entered the age of broad genomic analysis,<sup>10</sup> and there will be many more attempts to exploit this new knowledge for therapeutic gain. That is the hope for the future. Yet, the present reality is that even with the best available therapy, only a third of patients with limited-stage SCLC will survive beyond 5 years.<sup>7</sup> Despite all efforts to move forward, four cycles of etoposide plus cisplatin plus early, concurrent thoracic radiotherapy remains the standard of care for patients with limited-stage SCLC.

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Conflicts of interest statement to be added.

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