Dr. Alan Sandler’s sweeping review of the role of irinotecan (CPT-11, Camptosar) in the treatment of small-cell lung cancer (SCLC) leaves few stones unturned. Some perspective, however, is necessary. To date, with the exception of the Japan Clinical Oncology Group trial, which demonstrated the superiority of irinotecan in combination with cisplatin compared to standard therapy with etoposide and cisplatin, no other new platinum agent combination has proven superior to standard therapy in the treatment of extensive SCLC.[1] The Noda study, published recently in the New England Journal of Medicine, has sparked considerable interest and anticipation in the medical oncology community.

**Extensive-Stage, Chemonaive SCLC**

In a randomized phase III study, Noda and colleagues compared standard etoposide and cisplatin to an experimental regimen of irinotecan and cisplatin,[1] as piloted by Kudoh and others in Japan.[2] The study originally intended to randomize responders secondarily to either observation or radical thoracic radiotherapy (50 Gy in 2-Gy fractions per day × 5 weeks), but this component of the study was abandoned. Updated analyses demonstrated a significant benefit for irinotecan/cisplatin compared to etoposide/cisplatin, with 1- and 2-year survival rates, respectively, of 58.4% and 19.5% for the irinotecan-containing regimen vs 37.7% and 5.2% for the etoposide-containing regimen ($P = .0021$).

This difference could not be attributed to an imbalance in the delivery of treatment: 69% of those receiving irinotecan/cisplatin tolerated all four cycles, compared to 71% of those receiving etoposide/cisplatin. Also, there was no obvious discrepancy in baseline demographics. As expected, the irinotecan/cisplatin regimen produced significantly more grade 3 or higher diarrhea (16% vs 0%, $P = .001$) but significantly less neutropenia (66% vs 92%, $P = .0002$) and grade 3 or higher thrombocytopenia (5% vs 18%, $P = .01$).

Thus, in Japan, the irinotecan/cisplatin combination has become the standard for comparison in future studies of extensive disease. However, it should be noted that patients over age 70 were excluded, and the study precluded prior radiotherapy. Two separate North American trials alluded to by Dr. Sandler—one ongoing and one planned—will either refute or corroborate the Japanese results. An intergroup trial will recapitulate the Japanese effort, using identical doses. The other trial employs a more standard 3-week schedule, comparing etoposide (100 mg/m²/d × 3) and cisplatin (80 mg/m² on day 1) to irinotecan (65 mg/m² on days 1 and 8) and cisplatin (30 mg/m² on days 1 and 8) every 3 weeks.

The rationale for this altered schedule of irinotecan and cisplatin is fourfold: (1) elimination of day 15 irinotecan dosing, which was omitted or reduced in 50% of patients enrolled in the Japanese study; (2) symmetrical 3-week schedules for both arms; (3) reduced dose of cisplatin in an effort to reduce toxicity; (4) exploitation of putative cisplatin/irinotecan synergy using a weekly combination schedule. This study employs a 2:1 irinotecan/cisplatin vs etoposide/cisplatin randomization and targets a 50% 1-year and 15% 2-year survival rate for the irinotecan/cisplatin arm vs 37.5% and 7.5%, respectively for the control arm.

**Relapsed SCLC**

As Dr. Sandler points out, irinotecan has activity similar to that of topotecan (Hycamtin) in the relapse setting. In the only trial evaluating the role of irinotecan in previously treated SCLC, the response rate in 28 patients with refractory disease was only 3.7%, with a median time to
progression of 1.3 months and median survival of 2.8 months.[3] On the other hand, among the 17 patients with chemosensitive relapse accrued to this effort, the response rate was nearly 10-fold higher at 35%, with a median time to progression of 3.4 months and median survival of 5.9 months—virtually identical to the results of a pivotal randomized phase III trial comparing topotecan to the CAV regimen (cyclophosphamide [Cytoxan, Neosar], doxorubicin [Adriamycin], vincristine).[4] This critical distinction between chemorefractory and chemosensitive SCLC relapse has been observed with other agents as well, making it imperative that newer approaches for refractory patients be evaluated. Unfortunately, the majority of patients with extensive disease who relapse are no longer sensitive to additional cytotoxics.

Irinotecan/New Agent Combinations

Dr. Sandler alludes to new combinations of irinotecan that do not include standard cisplatin or carboplatin (Paraplatin). For example, in a small subset of patients enrolled in a phase II study of irinotecan and ifosfamide (Ifex), 8 of 11 with SCLC responded to the combination.[5] Bahadori et al[6] demonstrated preclinical synergy between irinotecan and gemcitabine (Gemzar) in SCLC cell lines. Rocha Lima and colleagues from the Medical University of South Carolina (Charleston) completed a phase I trial of irinotecan in combination with gemcitabine, demonstrating that both agents could be combined at nearly full dose.[7] The maximum tolerated dose of gemcitabine was 1,000 mg/m² on days 1 and 8, in combination with irinotecan, 100 mg/m² on days 1 and 8, every 3 weeks. Using this schedule, the Cancer and Leukemia Group B (CALGB) has almost completed accrual to a salvage trial in both chemosensitive and chemorefractory, relapsed SCLC. The results of this effort should be available in the next 6 to 12 months.

Limited-Stage SCLC

Integrating irinotecan into standard therapy for limited disease is a therapeutic challenge. Multiple studies have demonstrated the superiority of early concurrent chemoradiation, compared to delayed concurrent or sequential chemoradiation.[8] The use of two cycles of etoposide and cisplatin administered during thoracic radiation, followed by two additional cycles, has emerged as the standard of practice. Turrisi et al showed the superiority of concurrent twice-a-day radiotherapy with etoposide and cisplatin, compared to once daily fractionation.[9] A 5-year survival rate in excess of 25% has been observed. Although irinotecan in combination with cisplatin has demonstrated therapeutic superiority to a standard regimen in extensive SCLC, this advantage may be difficult to prove in limited disease. The risk of excess toxicity and the potential loss of efficacy cannot be dismissed.

Kinshita and colleagues conducted a phase I study of first-line irinotecan and cisplatin with concurrent thoracic radiotherapy in patients with limited disease, combining irinotecan on days 1, 8, and 15 every 4 weeks and cisplatin on day 1 with split-course radiotherapy, 2 Gy daily for 2 weeks, followed by a 2-week rest period every cycle.[10] The study accrued 17 patients, ranging in age from 43 to 74 years. The maximum tolerated dose of irinotecan with this schedule was 40 mg/m², and of cisplatin, 60 mg/m². Fatigue was dose-limiting; there was no grade 3 or higher diarrhea. Unsurprisingly, the overall response rate was high (93.6%). However, survival data are not yet available. Notably, this trial employed split-course thoracic radiotherapy, which in early radiation trials proved inferior to standard, uninterrupted thoracic radiotherapy.

The Radiation Therapy Oncology Group (RTOG) plans to initiate a pilot study integrating cisplatin and irinotecan on a weekly basis during uninterrupted twice-daily radiotherapy, followed by three additional cycles of combination irinotecan/cisplatin. A recently completed phase I trial at Fox Chase Cancer Center in locally advanced non-small-cell lung cancer demonstrated the safety of irinotecan at a dose of 30 mg/m²/wk × 7, in combination with cisplatin, 25 mg/m²/wk × 7, and full-dose standard, single daily thoracic radiotherapy to a total dose of 63 Gy.[11] These results strongly suggest that the integration of these two agents into the limited-disease SCLC setting should be feasible.

Summary

The enthusiasm for irinotecan must be tempered, to some extent, until ongoing and planned North American trials either confirm or refute the early Japanese data. Until then, irinotecan will not become part of standard induction therapy in treatment-naive SCLC. Nevertheless, the data to date are promising and demand further, aggressive evaluation.

References:


