Camptothecin and Taxane Regimens for Small-Cell Lung Cancer

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For more than 2 decades, combination chemotherapy has been the standard treatment for patients with small-cell lung cancer. Despite high initial response rates in both extensive- and limited-stage disease, long-term survival

The Centers for Disease Control and Prevention recently reported that the annual mortality for lung cancer in the United States is 154,000.[1] Small-cell lung cancer accounts for approximately 15% of these tumors. Over the past 2 decades, combination chemotherapy has become the standard of care for patients who present with extensive disease. Regimens such as EP (etoposide, cisplatin [Platinol]), CAV (cyclophosphamide [Cytoxan, Neosar], doxorubicin [Adriamycin], vincristine), and EC (etoposide, carboplatin [Paraplatin]) can produce response rates as high as 80%. Nevertheless, for patients with extensive-stage disease, the median survival is just 7 to 11 months and few patients are alive 2 years from diagnosis. Even in limited-stage disease, combined modality treatment with concurrent chemotherapy and radiation produces long-term survival in only 15% of patients.

As a result, evaluation of newer agents in treatment of small-cell lung cancer is of critical importance. Newer agents that are active in small-cell lung cancer include irinotecan (CPT-11, Camptosar), docetaxel (Taxotere), gemcitabine (Gemzar), ifosfamide (Ifex), paclitaxel, topotecan (Hycamtin), and vinorelbine (Navelbine).[2] In this article, we will focus on progress in the development of camptothecin/taxane combinations in the management of small-cell lung cancer.

Role of Camptothecin Derivatives in Small-Cell Lung Cancer

The mechanism of action of camptothecin analogs involves their interaction with topoisomerase I. As a result, the DNA/topoisomerase complex is bound and normal DNA replication is disrupted, leading to double-stranded DNA breaks and cell death. Semisynthetic compounds in this class include topotecan and irinotecan.

Irinotecan has shown activity against a broad range of animal and human malignancies, including lung cancer. In chemotherapy-naive small-cell lung cancer patients, Negoro et al reported a 50% response rate to single-agent irinotecan in a small series.[3] In previously treated small-cell lung cancer patients, response rates of 16% to 47% have been reported.[4] More recently, a Japan Clinical Oncology Group phase III trial of 152 extensive-stage small-cell lung cancer patients showed superiority of irinotecan/cisplatin over etoposide/cisplatin in terms of median survival (411 vs 282 days, \( P = .0021 \)), overall response rate (83% vs 68%), and 2-year survival rate (19% vs 7%).[5] Two North American phase III trials are under way to further define the role of irinotecan/cisplatin combinations in small-cell lung cancer.

Topotecan is the other approved semisynthetic camptothecin. Schiller et al treated 48 newly diagnosed extensive-stage patients with topotecan at 2 mg/m²/d for 5 days every 3 weeks. The response rate was 40% and median survival was 10 months.[6] Pooled data of 168 patients with sensitive relapse (defined as relapse occurring more than 3 months after previous chemotherapy) showed that 18% responded to topotecan with a median survival of 30 weeks and a 1-year survival rate of 21%.[7] A randomized trial comparing topotecan with CAV in patients with sensitive relapse demonstrated comparable response rates and survival times for the two regimens. In that study, topotecan was more effective in controlling disease-related symptoms.[8] In a recent Eastern Cooperative Oncology Group (ECOG) study of 223 patients with extensive-stage small-cell lung cancer, topotecan given after four cycles of EP improved progression-free survival by 1.3 months when compared to observation. However, overall survival and quality of life were not statistically different in the two arms.[9]
Role of Taxanes in Small-Cell Lung Cancer

The taxanes promote microtubular assembly but prevent their disassembly, thus interfering with normal tubulin polymerization and cell division. Both the Pacific yew-derived paclitaxel and the semisynthetic compound docetaxel show promise in the treatment of small-cell lung cancer.

The ECOG performed a phase II study of single-agent paclitaxel in previously untreated extensive-stage small-cell lung cancer patients. Paclitaxel at 250 mg/m² infused over 24 hours produced a response rate of 34%, but 56% of patients had grade 4 leukopenia.[10] The North Central Cancer Treatment Group used a similar paclitaxel schedule with the addition of granulocyte colony stimulating factor (G-CSF [Neupogen]) support and reported a 53% response rate and a reduction to 14% in the rate of grade 4 leukopenia.[11] In a small trial involving pretreated patients with early relapses, paclitaxel was associated with a 29% response rate.[12] When paclitaxel was combined with cisplatin, Nair et al reported impressive response rates of 71% to 89% in extensive-stage small-cell lung cancer patients.[13]

Docetaxel has also been studied for the treatment of small-cell lung cancer. In a phase II trial of chemotherapy-naive small-cell lung cancer patients conducted by the Southwest Oncology Group (SWOG), docetaxel at 100 mg/m² produced a response rate of 25% and a median survival of 9 months.[14] The European Organization for Research and Treatment of Cancer (EORTC) reported a response rate of 25% with single-agent docetaxel at a dose of 60 mg/m² in previously treated patients.[15]

Combinations of Docetaxel and Irinotecan

In animal and human cell lines, the combination of taxanes and camptothecins can be additive or synergistic, but results have been conflicting. Chou et al showed synergism between paclitaxel and topotecan in human teratocarcinoma cell line,[16] but Kaufman et al actually showed antagonism when this combination was used in a human lung cancer cell line.[17] In vitro studies of the combination of docetaxel and irinotecan showed notable activity in many models. There was the suggestion that their activity in combination may be dependent on dosing, sequencing, and cell type.

Couteau et al showed in a phase I study that when docetaxel was given prior to irinotecan, no relevant drug interaction was detected and the pharmacokinetics were consistent with the behavior of each drug given individually.[18] Takeda et al gave the irinotecan prior to docetaxel and reported a mild increase in docetaxel clearance.[19] The bulk of evidence suggests no clinically significant interaction between these two drugs with respect to pharmacokinetics.[18-21]

In terms of dosing schedule, initial studies administered the medications on an every 3-week cycle. However, high rates of neutropenia and late diarrhea were reported in such studies (see Table 1). Couteau et al reported 85% with grade 4 leukopenia lasting a median of 5 days (and 22.5% with febrile neutropenia).[18] Adjei et al reported 94% with grade 3/4 leukopenia and 17% with febrile neutropenia.[22] Masuda et al reported grade 3 or 4 neutropenia in only 19% with only 6% having febrile neutropenia, but this study employed lower dose intensity. Most phase II trials of docetaxel/irinotecan also report neutropenia as the most frequent toxicity.

When given with equivalent dose intensity, docetaxel on a weekly schedule has a lower incidence of neutropenia compared to a 3-week schedule. Additionally, more frequent administration allows the option of withholding doses when neutrophil counts are borderline. Additionally, irinotecan displays a more favorable toxicity profile when given on a weekly basis. Major toxicities of irinotecan when given on an every-3-week schedule tend to be granulocytopenia, febrile neutropenia, and/or late diarrhea. When given on a weekly schedule, irinotecan has lower incidences of severe neutropenia and diarrhea. Thus giving docetaxel/irinotecan combinations on a weekly schedule should be considered as a means of increasing the safety of administration.

At the Yale Cancer Center, we have conducted a phase I study evaluating weekly docetaxel/irinotecan. We originally delivered the medications weekly for 4 weeks on an every-6-week
cycle, but due to frequent treatment delays at day 21 due to neutropenia, we amended the dosing guidelines. We found that the combination was better tolerated when docetaxel at 35 mg/m² and irinotecan at 60 mg/m² were given on days 1 and 8 of an every-3-week cycle. In 44 patients studied, preliminary data show grade 3 or 4 neutropenia in 25% and only 1 patient had dose-limiting febrile neutropenia (2.3%). Diarrhea became the dose-limiting toxicity, but first-cycle grade 3 or 4 diarrhea was only present in 11.3%. Font et al, Vernejoux et al, and Seneviratne et al also reported reduced complications of neutropenia in weekly docetaxel/irinotecan regimens and various gastrointestinal toxicities then became dose-limiting toxicities.[21,23,24] Thus, weekly combinations appear to allow safer administration of docetaxel/irinotecan.

Phase II studies of docetaxel/irinotecan have been reported at least in abstract form for non-small-cell lung cancer, ovarian cancer, gastric cancer, pancreatic cancer, and mesothelioma.[25-29] Unfortunately, progress in the evaluation of small-cell lung cancer has been slower. Possible reasons include lower incidence of small-cell lung cancer patients compared to non-small-cell lung cancer, and preferential enrollment in standard regimen or other clinical trials (such as phase III studies of cisplatin/irinotecan). Nevertheless, studies of this promising combination should be pursued for patients with extensive disease.

Combinations of Paclitaxel and Irinotecan

Several phase I studies have also been performed evaluating the combination of paclitaxel and irinotecan (see Table 2).[30-34] Most studies have achieved similar dose intensity and use some variant of a weekly dosing schedule. The dose-limiting toxicity is commonly related to severe neutropenia. Interestingly, an early report by DeMario et al of paclitaxel dosed at 80 mg/m² followed by irinotecan at 30 mg/m² given weekly for 3 weeks on an every-4-week cycle was complicated by prolonged grade 4 lymphopenia in 4 of 4 patients, lasting a mean duration of 12.8 days.[30] Two patients (50%) developed fungal sepsis in the first cycle and their protocol required paclitaxel dose reduction. Two Japanese pharmacokinetic analyses of phase I trials show that paclitaxel increases the AUC (area under the concentration-time curve) of irinotecan and its metabolites (such as SN-38).[31,32]

Rushing et al performed a phase I/II trial evaluating weekly paclitaxel/irinotecan specifically in treating small-cell lung cancer.[33] They were able to escalate doses to a recommended dose of paclitaxel at 50 mg/m² and irinotecan at 60 mg/m² weekly for 3 weeks on an every 4-week cycle. However, out of 19 enrolled patients, grade 4 toxicities included sudden demise due to acute pulmonary embolus, septic shock in the setting of neutropenia, thrombocytopenia, and dehydration without diarrhea or vomiting. Out of seven patients evaluable for response, three (43%) had complete response and five had at least partial response (71%). A phase II study was initiated and results are pending; however, it was designed to administer paclitaxel/irinotecan immediately after induction therapy with etoposide/platinum, so it will be difficult to ascertain the contribution of the paclitaxel/irinotecan portion to the observed outcomes.

Other Combinations of Taxanes and Camptothecins

Several studies have investigated docetaxel and topotecan in a variety of solid tumors.[35-37] Pharmacokinetic analyses have shown that topotecan significantly reduced docetaxel clearance and led to increased neutropenia.[38] Glisson et al performed a phase I study which resulted in a recommendable dose of docetaxel 75 mg/m² on day 1 and topotecan 1.4 mg/m² on days 1 to 3 on a 21-day cycle with G-CSF support. They found one partial response in a small-cell lung cancer patient and plan a phase II study of their regimen.[37]

The two-drug combination of paclitaxel and topotecan has been studied since the mid-1990s. Lilienbaum et al reported that G-CSF allowed the maximum tolerated dose of paclitaxel to be increased from 80 to 230 mg/m² when given with a fixed dose of topotecan of 1.0 mg/m² for 5 days every 21 days.[39] In a phase I trial of 17 untreated small-cell lung cancer patients, Schnell et al recommended a dose of paclitaxel at 135 mg/m² on day 1 along with topotecan at 1.5 mg/m² on days 1 to 3 without G-CSF support.[40] The Cancer and Leukemia Group B (CALGB) enrolled 36 extensive-stage small-cell lung cancer patients in a phase II study of paclitaxel at 175 mg/m² on day
One study evaluated a sequential dose-dense schedule in this combination. Felip et al gave paclitaxel at 250 mg/m² on day 1 every 14 days for three cycles, followed by topotecan at 2.5 mg/m² on days 1 to 5 on an every-14-day cycle for three additional cycles. G-CSF was administered with each cycle. They reported an overall response rate of 73% (16 partial responses, 3 complete responses; 26 evaluable patients) and median survival of 10.5 months. In terms of toxicity, febrile neutropenia occurred in 19% (one toxic death [5%]), and only during the topotecan portion of therapy.[42]

Paclitaxel combined with topotecan and carboplatin in a three-drug regimen (PCT) has also been studied in the management of small-cell lung cancer. The combination of the three has overlapping toxicity in terms of myelosuppression that has limited the dosages of each drug that can be given. A recent phase II study by Hainsworth et al used the PCT combination as first-line therapy for 46 patients with limited-stage small-cell lung cancer and 59 patients with extensive-stage small-cell lung cancer.[43] They gave paclitaxel at 135 mg/m² on day 1, carboplatin at an AUC of 5 on day 1, and topotecan at 0.75 mg/m² on days 1 to 3 of a 21-day cycle. Limited-stage patients also received concurrent lung irradiation (to 45 Gy). Those with partial responses or stable disease after four cycles (82%) were then treated with an oral etoposide regimen (50 mg alternating with 100 mg/d for 10 days on a 21-day cycle) for three additional courses.

They reported impressive response rates of 88% for extensive-stage and 93% for limited-stage patients. The median survival for extensive-stage small-cell lung cancer patients was 8.3 months and for limited-stage patients it was 17.2 months. The protocol was tolerated fairly well by patients with good ECOG performance status (0/1), with the main toxicity being neutropenia (grade 3/4 in 45%) and thrombocytopenia (grade 3/4 in 20%). However, in the cohort of poorer performance status patients (ECOG 2), excessive toxicity was noted, with 5 of 12 patients (43%) suffering treatment-related deaths. The authors concluded that this PCT regimen did not appear to offer improvement in efficacy over standard EP regimens, but had greater morbidity.

The SWOG 9914 study also investigated the PCT combination as front-line therapy for extensive-stage small-cell lung cancer.[44] They administered paclitaxel at 175 mg/m² on day 4, carboplatin at an AUC of 5 on day 4, and topotecan at 1.0 mg/m² on days 1 to 4 every 21 days for six cycles. They enrolled 82 patients with ECOG performance status of 0 to 2, and have reported a median time to progression of 7 months, median survival of 12 months, and 1-year survival rate of 50%. Toxic deaths occurred in 7% of evaluable patients and common grade 3/4 toxicities included neutropenia (48%), thrombocytopenia (44%), anemia (15%), and nausea (12%). Given its promising survival data and acceptable toxicity profile, phase III trials are warranted. However, concerns about the hematologic morbidity of these regimens persist. One possibility in managing the restrictions of neutropenia is peripheral blood stem-cell support (PBSC). Schilder et al have explored higher-dose PCT with PBSC in the phase I setting, and shown an acceptable toxicity profile.[45] A phase II trial evaluating this regimen as front-line therapy for small-cell lung cancer is under way.

**Conclusion**

The current management of small-cell lung cancer remains frustrating. For many years clinical research failed to demonstrate a convincing advance beyond the results obtained with four to six cycles of cisplatin and etoposide. The recent Japanese Clinical Oncology Group study, if confirmed, provides hope that cytotoxic chemotherapy can be designed that will improve survival in this highly chemotherapy-sensitive disease. Taxanes and camptothecins in combination have shown promise in early trials and should be further studied in the future.

**References:**

1. Centers for Disease Control: Recent trends in mortality rate for four major cancer, by sex and


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