Irinotecan for the Treatment of Cervical Cancer

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Topoisomerase inhibitors have been widely studied for the treatment of refractory or recurrent cervical cancer. Various schedules have been used, with response rates ranging from 13% to 20%. The combination of cisplatin and irinotecan (CPT-11, Camptosar) is being studied in cervical cancer.

Topoisomerase inhibitors are essential nuclear enzymes with a multiplicity of cellular functions involving DNA replication, RNA transcription, mitosis, and chromosome condensation.[1] Two classes have been identified in mammalian cells: the class I topoisomerases, so named because such agents induce single-strand breaks and reunions of the DNA double helix; and the class II topoisomerases, so named because such agents induce double-strand breakage-reunion reactions with the DNA double helix. Both enzymes catalyze the interconversion of various topologic isomers of DNA.[2,3] Camptothecin, an alkaloid from the tree Camptotheca acuminata (Nyssaceae), is the parent compound of topotecan (Hycamtin), irinotecan (CPT-11, Camptosar), 9-aminocamptothecin, 9-nitrocamptothecin, and other analogs.[4] Topotecan and irinotecan are commercially available water-soluble derivatives of camptothecin. The active form of the camptothecins is the closed lactone ring, which is pH-dependent.[5] Preclinical activity screening of camptothecin and its analogs has been demonstrated in several models including gynecologic tumors. In addition, irinotecan is a prodrug and needs to be metabolized for optimal activity. A carboxylesterase catalyzes the conversion of irinotecan to its active metabolite SN-38 (7-ethyl-10-hydroxycamptothecin).[6] Using a subrenal capsule assay, irinotecan showed growth-suppressive effects of greater than 50% in two cervical cell lines.[7]

Camptothecin analogs also augmented the activity of cisplatin, fluorouracil (5-FU), and etoposide in HST-1, a human squamous cell carcinoma cell line.[8-11] This may result from inhibition of the removal of cisplatin DNA adducts.[10] These compounds appear to have radiosensitization properties in small-cell and adenocarcinoma lung cancer cell lines,[12] which has also been demonstrated in patients.[13] The addition of recombinant tumor necrosis factor and irinotecan to several gynecologic cancer cell lines also demonstrated synergistic effects.[14]

First-Line Treatment of Cervical Cancer

Therapy for cervical cancer is chosen according to the clinical stage. Most patients with early-stage disease (IA, IB1) are cured by surgery or radiotherapy; chemotherapy has no role in this setting.[15] For patients with higher-stage disease (IB2 to IVA) or positive lymph nodes, chemoradiation is the treatment of choice.[16] Irinotecan has not been studied in combination with radiotherapy for the treatment of cervical cancer. In animal studies, however, the combination is synergistic.[12] Experimental modalities for the primary treatment of cervical cancer stages IB to IVA include neoadjuvant chemotherapy followed by radical surgery.[17] Sugiyama et al tested the combination of cisplatin (60 mg/m² on day 1) and irinotecan (60 mg/m² on days 1, 8, and 15) administered prior to surgery to 23 patients with stage IB2 to IIIB cervical cancer. The patients were chemotherapy-naïve and had a median age of 59 years. Eighty-seven percent of patients had squamous cell histology. The overall response rate was 78%, with 3 complete remissions, 15 partial remissions, 4 stabilizations, and 1 progression of disease. Median survival has not yet been reached.[18]

Systemic Therapy for Refractory Disease

In contrast to the first-line setting, chemotherapy is used to treat recurrent or metastatic cervical cancer. Single-agent chemotherapy yields survival benefits similar to that of chemotherapy combination regimens; single-agent treatment is preferred because it is associated with fewer side effects.[19] Response rates to single agents vary from 15% to 30% and complete responses are rare. Cisplatin and carboplatin (Paraplatin) are considered the most active single drugs. Patients with renal
failure or poor performance status rarely benefit from chemotherapy. Combination chemotherapy has been tested in numerous trials. While high response rates have been documented even in heavily treated patients, response durations are short and survival is not improved over that achieved with single-agent treatment. Furthermore, results from randomized trials comparing single-agent and combination therapy demonstrated no significant benefits for the combination.[20]

**Single-Agent Trials**

Irinotecan is the only active agent in platinum-refractory disease.[21] This agent has been tested as a single agent in cervical cancer patients refractory to platinum-based therapy in five trials (Table 1). The first phase II trial in the United States used a schedule of 125 mg/m²/wk for 4 weeks followed by a 2-week rest. A total of 42 patients with a median age of 44 years (range: 24-59 years) were treated for a median of 2 cycles (range: 1-14 cycles). All patients had failed previous chemotherapy. The response rate was 21% with a median time to response of 6 weeks and a response duration of 12 weeks. The major dose-limiting side effects were nausea and vomiting (45%), diarrhea (24%), and myelosuppression (36%). Myelosuppression did not decrease when the irinotecan dose was reduced, whereas gastrointestinal side effects did. The investigators concluded that irinotecan had significant clinical activity and warranted further investigation, although hematologic and gastrointestinal side effects were problematic.[22]

The Gynecologic Oncology Group (GOG) conducted another trial of single-agent irinotecan in 54 patients with recurrent or refractory disease. Most patients had received previous radiotherapy and 12 had also received chemotherapy. Of 45 evaluable patients for response (49 for toxicity), 6 (13%) responded, including 1 with a complete response. Grade 3/4 gastrointestinal toxicity occurred in 19 (39%) patients. The authors concluded that the drug had modest activity and moderate toxicity, and should be combined with cisplatin for future study.[23]

In one study of irinotecan in patients with recurrent cervical cancer, no response was observed. However, a few patients had subjective improvement and the authors conclude that further exploration of this drug was warranted.[24]

The European Organization for Research and Treatment of Cancer (EORTC) has conducted a trial of irinotecan as primary chemotherapy in cervical cancer. Patients were stratified according to whether measurable disease was present outside (group A) or within (group B) the previously radiated area. Irinotecan at 350 mg/m² was administered every 3 weeks. Responses occurred in 5 of 21 (24%) group A patients and in none of the 13 group B patients, for an overall response rate of 15%. The duration of response was 6+ months. However, two patients died from toxic effects related to myelosuppression, diarrhea, or dehydration. The authors recommended further studies to define better the gastrointestinal side effects.[25]

The Japanese have had extensive experience with irinotecan in gynecologic cancers. In one study of 24 patients who received 100 mg/m² weekly for four doses, 5 (21%) responded. Among another 31 patients who received 150 mg/m² every 2 weeks for three courses, 8 (26%) responded. It is notable that the majority of patients in both groups had received previous radiotherapy and chemotherapy. Myelosuppression and gastrointestinal side effects were significant and treatment-related deaths occurred. No recommendation was made regarding further study.[26,27]

Irinotecan has not been extensively studied in combination with other agents in the treatment of cervical cancer. Sugiyama et al studied irinotecan given on days 1, 8, and 15, combined with cisplatin administered on day 1 only. Cycles were repeated every 29 days. The recommended doses were cisplatin at 60 mg/m² and irinotecan at 60 mg/m². Of 29 patients treated, 17 (59%) had major responses.[28] There is also potential for this combination to be applied in the neoadjuvant and adjuvant settings.[29]

**Conclusions**

The topoisomerase I inhibitors have not been extensively studied in some gynecologic cancers. Single-agent activity is definite but modest with all of the analogs. Most investigators recommend studying the combination of irinotecan and cisplatin, and such studies are underway. Laboratory data indicate potentially interesting interactions of irinotecan with radiotherapy and cytokines. Such findings need further refinement within the conduct of correlative clinical studies.

**References:**


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