Irinotecan in Epithelial Ovarian Cancer

Ovarian cancer, the second most common gynecologic malignancy, accounts for approximately 14,000 deaths annually in the United States. Disease relapse after primary treatment, which consists mainly of surgery followed by platinum-based therapy, occurs in more than 60% of ovarian cancer patients overall, and in more than 80% of those diagnosed initially with advanced-stage disease.

Ovarian cancer is the second most common gynecologic malignancy, accounting for approximately 23,400 cases annually in the United States.[1] Although it is only the fifth most common cancer among women in the United States, its importance is far out of proportion to its incidence because it is the most lethal of gynecologic cancers. Approximately 13,900 women die from ovarian cancer annually in the United States.[1]

Because no effective screening method exists for ovarian cancer, more than 70% of women are diagnosed when the cancer has already spread beyond the ovary. Standard treatment for the majority of patients with epithelial ovarian cancer consists of primary surgery followed by platinum-based chemotherapy. The current standard regimen is the combination of paclitaxel and carboplatin (Paraplatin).[2]

Survival rates for patients with stage III and IV epithelial ovarian cancer are approximately 15% to 20% and less than 5%, respectively. Therefore, more than 60% of patients with ovarian cancer, regardless of stage, and more than 80% of those with advanced-stage epithelial ovarian cancer, will have disease relapse following primary treatment. In general, recurrent ovarian cancer is incurable, partly because of the relative inefficacy of salvage therapy.

Patients with recurrent ovarian cancer are not a homogeneous group. To date, the probabilities of responsiveness and outcome are related to a variety of clinicopathologic factors. One of the strongest predictive factors is the length of time from completion of primary chemotherapy to relapse.[3-6] This observation has led to definitions of platinum sensitivity and platinum resistance.[7]

Currently, conventional chemotherapeutic agents constitute the predominant option for secondary therapy. However, in the setting of platinum-resistant ovarian cancer, response rates associated with the most active agents, including topotecan (Hycamtin),[8-10] liposomal doxorubicin (Doxil),[11,12] gemcitabine (Gemzar),[13,14] vinorelbine (Navelbine),[15-17] and oral etoposide,[18] range from 15% to 25%. Most responses are partial and not durable. Therefore, a concerted effort to identify new active agents—both chemotherapeutic and nonchemotherapeutic—against epithelial ovarian cancer is justified.

Irinotecan Chemotherapy in Ovarian Cancer

Irinotecan is a derivative of camptothecin and belongs to a class of chemotherapeutic agents that inhibit topoisomerase I. Topoisomerase I is a protein with enzymatic activity that relaxes supercoiled double-strand DNA, thereby permitting DNA replication and RNA transcription.[19] Clinical development of irinotecan began in Japan in the 1980s. Subsequent preclinical studies demonstrated that it had antitumor activity in ovarian cancer.[20-23] O'Meara and Sevin found that the median effective doses of irinotecan were significantly lower than clinically achievable peak plasma concentrations in 7 of 12 fresh ovarian carcinoma specimens, and 11 of 12 specimens showed sensitivity to the active metabolite SN-38.[22]

Single-Agent Irinotecan Studies

Early clinical trials of irinotecan in ovarian cancer patients were conducted almost exclusively in Japan. In 1991, Takeuchi et al reported results of a phase II trial of irinotecan in 15 patients with recurrent ovarian cancer.[24] Three drug schedules were used, including 100 mg/m² weekly, 150 mg/m² every 2 weeks, and 200 mg/m² every 3 to 4 weeks. The authors reported one complete
response and two partial responses, for an overall response rate of 20%. Significant toxicities were reported among the 30 patients in the study, which also included cervical and uterine cancer patients. Leukopenia occurred in 30% of patients, anemia in 20%, and nausea and vomiting in 13%. Subsequently, the same researchers reported results of a late phase II study in which 55 patients with ovarian cancer received irinotecan in one of two schedules: 100 mg/m² weekly (regimen I) or 150 mg/m² every 2 weeks (regimen II).[25] Thirteen partial responses were observed, for a response rate of 24%. A total of 24% of patients receiving regimen I and 14% receiving regimen II responded. Major toxicities again included leukopenia in 57%, anemia in 25%, and diarrhea in 19% of patients. At the American Society of Clinical Oncology annual meeting in 1997, Sugiyama and colleagues reported results of a phase II study of irinotecan in 52 patients with refractory ovarian cancer.[26] Patients were randomly assigned to one of two dose schedules: 100 mg/m² weekly (regimen I, 27 patients) or 150 mg/m² every 2 weeks (regimen II, 25 patients). Response rates were 29.6% for regimen I and 16% for regimen II. The authors noted that responses occurred among patients with mucinous and clear cell tumors, which are known to be relatively chemoresistant. The dose-limiting toxicity was leukopenia, which was observed in 57% of patients. Grade 3 or worse diarrhea was noted in 19.2% of patients.

A phase II study of irinotecan alone in patients with platinum-resistant epithelial ovarian cancer was presented at the American Society of Clinical Oncology annual meeting in 2001.[27] That study has now been completed, and a manuscript has been submitted for publication.

Irinotecan in Combination Chemotherapy for Ovarian Cancer

Irinotecan has also been studied in combination with other chemotherapy drugs in ovarian cancer patients. Shimizu et al reported results of a trial of irinotecan plus mitomycin (Mutamycin) in 10 patients with newly diagnosed clear cell cancer of the ovary.[28] Irinotecan at 140 mg/m² was administered on days 1, 15, and 29, and mitomycin at 7 mg/m² intraperitoneally (IP) on days 1, 15, and 29. Treatment cycles were repeated every 4 weeks. The authors observed a 60% response rate in this chemoresistant tumor type, with four complete responders and two partial responders. The most commonly studied irinotecan combination has been irinotecan plus cisplatin. Adachi et al conducted a phase II study of irinotecan plus cisplatin in 10 patients with newly diagnosed clear cell cancer of the ovary.[29] Doses included irinotecan at 60 mg/m² on days 1, 8, and 15, and cisplatin at 70 mg/m² IV on day 1 (three patients) or 75 mg/m² IP on day 1 (seven patients). The overall response rate was 20%, with one complete response and one partial response. Toxicities included grade 3 leukopenia in 70% and grade 3 diarrhea in 10% of patients.

Sugiyama et al reported results of a phase II trial in which 25 patients with recurrent ovarian cancer received the irinotecan/cisplatin combination.[30] Doses were irinotecan at 50 to 60 mg/m² on days 1, 8, and 15, and cisplatin at 50 to 60 mg/m² on day 1. Four of the 25 patients were platinum-sensitive and 21 were platinum-resistant. The overall response rate was 40%, with a complete response rate of 8%. When subgroups were considered, the response rate for platinum-sensitive patients was 75%, and the response rate for platinum-resistant patients was 33%. Again, the authors noted patients with clear cell or mucinous tumors among responders. The median duration of response was 5.5 months. Grade 3 or 4 neutropenia was observed in 55% of cycles and 64% of patients, and grade 3 or 4 diarrhea was noted in only 3% of cycles and 4% of patients.

In another study of the irinotecan/cisplatin combination, 30 patients with recurrent ovarian cancer received irinotecan at 50 to 60 mg/m² on days 1, 8, and 15, and cisplatin at 60 mg/m² on day 1.[31] The response rate was 60%, with two complete responses and 16 partial responses. The study included 12 platinum-sensitive and 18 platinum-resistant patients. Apparently, the response rate was 60% in both subgroups.

Conclusion

In summary, irinotecan has moderate activity and acceptable toxicity in patients with recurrent epithelial ovarian cancer. Although data suggest that the weekly irinotecan schedule is associated with a superior response rate compared with the other schedules, no randomized data are available to support this. Other well-designed confirmatory trials of irinotecan are needed. Dose-limiting toxicities appear to be diarrhea, nausea and vomiting, and leukopenia/neutropenia. However, the bone marrow toxicity of irinotecan appears to be significantly less than that associated with topotecan. Furthermore, gastrointestinal effects have been tolerable for most patients when managed with a combination of supportive care and dose reduction.
References:


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