Irinotecan in Lymphoma, Leukemia, and Breast, Pancreatic, Ovarian, and Small-Cell Lung Cancers

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Irinotecan (CPT-11 [Camptosar]) has a broad range of antitumor activity. Extensive preclinical and early clinical work has demonstrated its activity against many tumor types--head and neck, esophagus, stomach, pancreas,

**Introduction**

Extensive preclinical work has demonstrated the efficacy of irinotecan (CPT-11 [Camptosar]) against many cancer cell lines and human tumor xenografts. In addition, numerous phase I clinical trials have included case reports of responses in different tumor types. Minor, partial, and/or complete responses to varying schedules of irinotecan have been reported in patients with cancers of the head and neck, esophagus, stomach, pancreas, liver, colon/rectum, kidney, lymph nodes, ovary, and uterine cervix. [1-8] These papers also have described responses in sarcoma, melanoma, acute and chronic leukemia, mesothelioma, and cancers of unknown primary site. Isolated cases are helpful in the design of future phase II trials but, of course, need to be interpreted with caution.

Most of the phase II and III trials of irinotecan have been conducted in patients with colorectal and other gastrointestinal, non-small-cell lung, and cervical cancers. These trials are discussed in other articles in this monograph. This article discusses the limited number of studies of irinotecan in other diseases. Specifically, phase II trials in lymphoma, leukemia, breast, pancreas, ovarian, and small-cell lung cancers are presented.

As will become evident from this discussion, the information gleaned from such preliminary work is subject to many limitations. The number of patients enrolled in the studies is small, and often patients with different disease histologies, stages, and number of prior treatments are included, thereby diluting the reproducibility of the results even further. In many of the early Japanese trials, two or sometimes more dosing regimens are employed in the same trial. When response or toxicity information is eventually reported, rates are based on numbers of patients evaluable rather than number of patients enrolled. Many patients, either because of advanced disease and/or extreme toxicity, are not included in the efficacy analysis.

Most of the trials discussed in this article have been published in abstract form only, itself a limitation on the amount of information that can be presented. When several publications appear in the same year with similar but not identical lists of authors, one cannot be sure whether two separate trials are being summarized or whether the same study is being updated with additional patient numbers. Finally, response duration or length of survival often is not presented, limiting the value of the information that is included.

Despite these drawbacks, which are fairly typical of preliminary data, these studies contain some interesting information. They appear to show a broad range of clinical activity of irinotecan. These studies leave much room open for further study to discover the precise diseases in which the drug may be useful and in which combinations.

**Lymphoma**

Several phase I trials hinted that irinotecan has clinical activity against the lymphomas; these included one complete response in a patient with previously treated non-Hodgkin’s lymphoma who received 500 mg/m² every 3 weeks. [9] Often, such publications did not provide precise details about disease histology, previous treatment, response duration, and survival. A few phase II trials,
conducted in Japan, were limited in that they involved patients with several histologic types and degrees of prior therapy. Two previously published trials included patients with both non-Hodgkin’s lymphoma and Hodgkin’s disease, and one of these studies also included patients with acute leukemias. (With regard to the latter study, the lymphoma patients will be discussed here and the leukemia patients, in the following section.)

**Irinotecan Alone**

Ohno et al described a series of 29 patients with non-Hodgkin’s lymphoma and 3 with Hodgkin’s disease enrolled at 14 Japanese institutions between December 1987 and October 1989.[10] This study population included 3 patients with follicular lymphoma, 2 with diffuse small-cell lymphoma, 7 with diffuse medium-cell lymphoma, 2 with diffuse mixed large- and small-cell lymphoma, 10 with diffuse large-cell lymphoma, 4 with lymphoblastic lymphoma, and 1 with an immunoblastic lymphoma. The Hodgkin’s disease patients were not characterized by subtype. Although not specifically mentioned in the study, it can be assumed that all of the patients were pretreated, as 10 were characterized as primarily refractory and 21 as both relapsed and refractory.

In the initial treatment phase of the study, patients were randomly assigned to 200 mg/m² of irinotecan every 3 to 4 weeks (schedule A) or 40 mg/m² for 5 days every 3 to 4 weeks (schedule B). An interim analysis showed no response to the first dosing regimen and early relapses (ie, before recovery of normal hematopoietic cells) in patients given the second regimen. Subsequent patients, therefore, were randomized to 40 mg/m² of irinotecan for 3 days every week (schedule C) or 20 mg/m² twice daily for 7 days every 3 to 4 weeks (schedule D).

Results by histology are detailed in Table 1 and by schedule in Table 2. Overall response rates were 24% in the non-Hodgkin’s group (four complete and three partial responses) and 33% in those with Hodgkin’s disease (one partial response in three patients). Toxicities were predictable, with myelosuppression, diarrhea, nausea, vomiting, and anorexia being the most common.

The authors concluded that a single monthly dose of irinotecan was ineffective for these diseases and that only divided doses given daily (for 3 or 7 days) produced responses. These conclusions are consistent with the theoretical notion that a mechanism of action dependent on cell proliferation would require more frequent dosing.

A follow-up phase II study in lymphoma, conducted by the same group, was published in 1992.[11] This phase II study enrolled 59 patients (56 evaluable for toxicity and 51 for efficacy) who were treated with the prior study’s schedule C, 40 mg/m² of irinotecan for 3 days repeated weekly. Again, multiple histologies were included, with 44 patients described as having non-Hodgkin’s lymphoma, 8 having adult T-cell leukemia/lymphoma (ATLL), and 4 having Hodgkin’s disease. The patients appear to have been heavily pretreated, and had fairly good Eastern Cooperative Oncology Group (ECOG) performance status.

In the non-Hodgkin’s group, 8 complete and 15 partial responses were recorded (44%); no responses were noted in the Hodgkin’s group. Interestingly, there was a 50% response rate (four partial responses) in the ATLL group. The regimen was reasonably well tolerated in this trial.

The results of this trial were updated by Ota et al in 1994.[12] Of 79 patients with lymphoma, 66 completed treatment. The overall response rate was 42% (95% confidence interval [CI], 30% to 54%), including nine complete responses in patients with non-Hodgkin’s lymphoma and no responses in the four individuals with Hodgkin’s disease. The ATLL subgroup of NHL patients (reported separately in another publication[13]) had a response rate of 39% (one complete response, four partial responses).

**Irinotecan Combined With Carboplatin**

The Japanese study group conducted a phase I/II trial in which carboplatin (Paraplatin) was added to irinotecan.[14] Irinotecan was given at a dose of 20 mg/m² for 3 days every week (with dose escalation planned), and carboplatin dose was fixed at 300 mg/m² on day 1. The first dose level was declared to be the maximum tolerated dose (MTD). In the eight patients treated at that level, the...
response rate was 25%, which was clearly not superior to the response rate achieved with irinotecan alone. As a result, the regimen was not pursued further.

Summary

The limited studies conducted to date (Table 3) suggest evidence of irinotecan’s activity against a number of lymphoma subtypes, albeit with numbers too small to answer questions with sufficient statistical power. No trials have examined the irinotecan dosing regimens currently approved for other diseases in the United States and Europe. Controlled investigations in patients with similar lymphoma subtypes and amounts of prior therapy should clarify the role of irinotecan, alone and in combination, in lymphoma.

Leukemia

Preclinical activity and early phase I data suggested that acute and chronic leukemias are responsive to irinotecan. The same study groups discussed above in the lymphoma section also enrolled patients with acute leukemias.

The report by Ohno et al described 11 patients with acute lymphoblastic leukemia (ALL) and 15 patients with acute myelogenous leukemia (AML, nearly all subtypes), all of whom had received prior treatment.[10] None of these patients responded to the first three irinotecan regimens detailed above (schedules A, B, or C); schedule D, 20 mg/m² twice daily for 7 days every 3 to 4 weeks, produced one complete response (in ALL) and two partial responses (one in ALL and one in AML subtype M3). Response rates, thus, were 18% in ALL and 7% in AML. Toxicities were not reported separately for the leukemia patients.

The update of these data by Ota et al included 50 patients with acute leukemia treated with irinotecan 15 to 20 mg/m² twice daily for 7 days every 2 to 4 weeks (41 of whom completed therapy).[12] Of 17 patients with ALL, 2 showed a partial response (12%); no responses were seen in the 24 patients with AML.

Based on these very limited studies, it appears that irinotecan has little activity against the acute leukemias. The studies to date provide little or no information on the efficacy of different dosing schedules, combinations of irinotecan with other drugs, or the use of the drug in patients with earlier-stage disease. If, in fact, responses have been seen in low-grade lymphomas, as discussed this suggests the possible value of irinotecan in such diseases as chronic lymphocytic leukemia or multiple myeloma. There is, of course, room for further study.

Breast Cancer

In nude mice, irinotecan showed activity in breast cancer human xenografts.[15] Early phase I studies of the drug in humans also revealed some partial responses in patients with breast cancer.[16] Clinical trials specific to breast cancers are summarized in Table 4.

In 1994, a Japanese multicenter group enrolled 25 patients with advanced or recurrent breast cancer in a phase II trial of three different dosing regimens: 100 mg/m² weekly (schedule A), 150 mg/m² biweekly (schedule B), or 200 mg/m² every 3 to 4 weeks (schedule C).[17] The overall response rate was 16% (four partial responses altogether), with schedule C achieving the highest response rate (3/15 patients with partial responses, 20%). Since, as predicted, schedule C produced the greatest toxicity, the 100-mg/m² weekly regimen (which produced one partial response in seven patients, 14%) was suggested for further trials.

In a second Japanese phase II study reported by Taguchi et al in the same year,[18] 65 patients with advanced breast cancer (of 75 enrolled) were treated with irinotecan, 100 mg/m² weekly. The overall response rate was 23% (1 complete response, 14 partial responses), with equivalent response rates observed in patients who had received prior hormonal therapy (11/41, 27%) or prior cytotoxic chemotherapy (12/46, 26%). Responses were also seen in patients with soft-tissue as well as bone metastases.
Bonnetere et al also conducted a phase II trial in which 29 patients who had received one prior chemotherapy regimen for advanced breast cancer were treated with 350 mg/m² of irinotecan every 3 weeks.[19] Of 12 evaluable patients described in their abstract, three were removed from the study due to toxicity. One patient with multiple soft-tissue sites of metastasis had a complete response, and four other patients exhibited stable disease. An update of these results has not yet been published.

Many cytotoxic drugs are active in advanced breast cancer, itself a very common disease. The studies described above demonstrate genuine activity of irinotecan, but do not address all of the commonly used dosing schedules or combinations of drugs. Obviously, further study is needed in this disease as well.

Pancreatic Cancer

Two phase II trials describing the activity of irinotecan in patients with pancreatic cancer have been reported ([Table 5](#)). Sakata et al enrolled 57 patients with advanced disease, 22 of whom had received prior chemotherapy.[20] These patients were treated with either 100 mg/m² of irinotecan once a week or 150 mg/m² every other week. In the 35 patients evaluable for response, the overall response rate was 11.4% (95% CI, 0.9% to 21.9%). Only the usual side effects were seen.

Another group published the results of a phase II trial in patients with advanced, previously untreated pancreatic cancer.[21] A total of 34 eligible patients (32 of whom were evaluable for response) received 350 mg/m² of irinotecan every 3 weeks. Only three patients had partial responses (response rate 9%; 95% CI, 3% to 25%); the duration of response was approximately 7.5 months in each patient. Toxicities were as expected and were easily managed.

Although only two trials with small numbers of patients have been reported in pancreatic cancer, they suggest that irinotecan has only modest activity. If irinotecan is pursued further in this disease, future trials should examine other dosing schedules and combinations.

Ovarian Cancer

Irinotecan Alone

Irinotecan has demonstrated activity against ovarian cancer cell lines and in human tumor xenografts.[22,23] The limited clinical trials in humans have suggested promise as well ([Table 6](#)), but by no means define the role of this drug in the treatment of advanced or early stage disease.

In 1991, Takeuchi et al reported, in both abstract form and a full-length journal article, the results of an early phase II trial of irinotecan in gynecologic cancers, including 14 patients with ovarian cancer, 4 with cervical carcinoma, 6 with uterine adenocarcinoma, and 1 with an endometrial stromal sarcoma.[24,25] These patients received one of three dosing regimens: 100 mg/m² weekly, 150 mg/m² every other week, or 200 mg/m² every 3 to 4 weeks.

There were two complete responses and one partial response in the patients with cervical cancer (response rate, 43%), one complete response and two partial responses in those with ovarian cancer (21.4%), and no responses in those with uterine cancers. Although all of the patients were pretreated, no information was provided on either the prior dosing regimens or the patients who were enrolled in the trial but were not included in the efficacy analysis.

A later phase II trial by the same group also was published in 1991.[26] This trial included 55 patients with cervical cancer and 55 patients with ovarian cancer who were given either 100 mg/m² of irinotecan weekly or 150 mg/m² every other week.

The response rate for both cancers was 23.6% (95% CI, 12.4% to 34.8%), with five complete responses and eight partial responses in cervical cancer and 13 partial responses in ovarian cancer. In the latter group, responses were seen in several different subtypes of ovarian cancer and in those
with primary lesions, as well as in distant metastases. There was nothing unusual about the side effects profile of irinotecan in this usually heavily pretreated population. Both dosing schedules were found to be effective.

A final series was published in abstract form by Sugiyama et al in 1997.[27] They randomly assigned 52 patients with recurrent ovarian cancer to the same two dosing regimens (100 mg/m² of irinotecan weekly or 150 mg/m² every other week). Response rates to the two regimens were 29.6% and 16%, respectively, and median survival time was 233 days.

Irinotecan in Combination Regimens

Trials of irinotecan in combination with other cytotoxic drugs have also been reported in ovarian cancer patients. Sugiyama's group conducted a phase I trial of irinotecan and cisplatin (Platinol).[28] In this trial, seven patients who had received no prior therapy for recurrent disease (although four had received adjuvant therapy) and five who had received prior therapy were treated with 50 to 60 mg/m² of cisplatin every 3 weeks and 50 to 60 mg/m² of irinotecan weekly. The DLT was neutropenia; 60% of patients had grade 3 or 4 neutropenia, which resolved shortly after administration of granulocyte colony-stimulating factor (G-CSF [Neupogen]). Of the 12 patients enrolled, 5 (41.7%) responded to the treatment regimen.

The same group performed a phase II trial using the identical treatment regimen in 18 patients.[29] Again, over half of the patients had grade 3 or 4 neutropenia, which resolved with G-CSF therapy, and nearly one third of all patients required the omission of at least one irinotecan dose. The overall response rate was 54.5%, with response durations of 2, 4, 6.5, 7, and 11.5 months at the time of the report.

The series was updated for the 1997 meeting of the American Society of Clinical Oncology, with similar response rates (40%) reported in a group of 20 patients.[27] In this update, the incidences of grade 3 or 4 thrombocytopenia (5.5%) and diarrhea (1.9%) were low.

Two other combinations have also been tested. Shimizu et al studied 20 patients with clear cell adenocarcinoma of the ovary, a disease that traditionally has been refractory to chemotherapy.[30] Irinotecan was given every other week at a dose of 140 mg/m², and mitomycin (Mutamycin) 7 mg/m² was given via intraperitoneal injection every other week. Of the 20, 12 patients had received prior chemotherapy, and 8 had not. The overall reported response rate was 60%, with the responders surviving significantly longer than the nonresponders (22 vs 7 months; P < .001).

In a brief case report, two patients tolerated the combination of irinotecan (75 mg/m² weekly) and carboplatin (75 to 100 mg/m² weekly); both had a partial response.[31] Major side effects were predictably leukopenia and thrombocytopenia.

Summary

These several preliminary trials show the promising activity of irinotecan in ovarian cancer, akin, perhaps even similar, to that of topotecan (Hycamtin), which is widely used in the disease. There appears to be little difference in response rate among the different single-agent irinotecan dosing schedules used. Future studies should examine the drug's effect in a more uniform patient population and should employ the dosing schedules currently approved in other diseases, alone and in combination with other active drugs.

Small-Cell Lung Cancer

Irinotecan Alone

Many investigators have reported the results of in vitro or in vivo studies evaluating the activity of irinotecan in lung cancers. Most of this work has centered on non-small-cell lung cancer and is presented elsewhere in this monograph. This article will describe the clinical studies published to date in patients with small-cell lung cancer (Table 7).
Negoro et al first published the results of a phase II study of irinotecan in 1991.[32,33] According to this abstract and subsequent journal article, 41 patients with small-cell lung cancer (33 previously treated and 8 untreated patients) were given 100 mg/m² of irinotecan weekly. Of the 41 patients, 35 were evaluable for response. Overall response rates were 33.3% in the previously treated group and 50% in the untreated group. Median duration of response was 50 days (range, 28 to 116 days), and toxicities were fairly predictable.

Shortly thereafter, Masuda’s group reported another phase II trial of 15 heavily pretreated patients given 100 mg/m²/wk of irinotecan.[34] Seven of these patients had had a complete response to prior chemotherapy, and eight were primarily refractory. In 14 patients, the interval between their last chemotherapy regimen and the initiation of irinotecan therapy was more than 90 days.

Overall, seven patients (47%; 95%, CI 21.4% to 71.9%) had partial responses to irinotecan, lasting a median of 58 days (range, 28 to 156 days). Median survival was 187 days. Interestingly, two patients with brain metastases at the time of entry responded to irinotecan.

Major toxicities were leukopenia and diarrhea. Also, two cases of grade 3 or 4 pneumonitis were reported. Pulmonary toxicity has been described in other phase I/II trials in Japan[35,36] but not in other studies.

Le Chevalier et al recently described a phase II study in small-cell lung cancer using the European dosing regimen of 350 mg/m² of irinotecan every 3 weeks.[37] This study enrolled 31 patients, all of whom had received one prior etoposide-based chemotherapy regimen. There were five objective responses (16%), including one complete response in a patient with brain metastases. Median response duration was 131 days (range, 51 to 266 days), and overall survival time was 125 days (range, 6 to 458+ days).

All of these single-agent studies demonstrate the activity of irinotecan in what usually is a chemotherapy-sensitive disease. Isolated patients in these trials have exhibited durable responses, indicating the need for expanded clinical trials of these and other dosing schedules.

**Irinotecan in Combination Regimens**

Combination trials in small-cell lung cancer have been reported as well. Irinotecan (starting dose, 60 mg/m² on days 1, 8, and 15) was combined with etoposide (80 mg/m² days 1 to 3 every 4 weeks) in a phase I study of patients with all types of lung cancer.[38] Granulocyte colony-stimulating factor (2 µg/kg) was administered on days 4 to 21, except on days when irinotecan was infused. The MTD of irinotecan was 80 mg/m², recommended dose was 70 mg/m², and the DLTs were, predictably, diarrhea and leukopenia. In the 14 patients with small-cell lung cancer, a response rate of 58% was reported. A follow-up trial in small-cell lung cancer has not been published.

Fujiwara et al conducted a phase II trial of irinotecan plus cisplatin in small-cell lung cancer.[39] In this trial, 75 previously untreated patients received cisplatin, 60 mg/m² on day 1, and irinotecan, 80 mg/m² on days 1, 8, and 15. After 3 of the first 10 patients experienced severe toxicity (diarrhea, leukopenia, and hepatic damage), subsequent patients received 60 mg/m² of irinotecan.

A total of 32 patients were evaluable for response; 18 with limited-stage disease, and 14 with extensive-stage disease. Response rates were 78% (four complete and 10 partial responses) in the limited-stage patients and 79% (3 complete and 8 partial responses) in the extensive-stage patients. Overall, 41% of patients experienced grade 3 or 4 leukopenia and 22% had grade 3 or 4 diarrhea. No pulmonary toxicity was seen, and median survival had not been reached at the time of the abstract’s publication.

**Other Cancers and Future Directions**

Except in the phase I setting, very few studies of irinotecan in cancers other than those discussed above have been published. Many trials are currently under way in the diseases already discussed...
and in others with even more limited phase I data available.

In terms of single-agent studies, most future work will focus on irinotecan doses currently approved in the United States (125 mg/m² weekly for 4 weeks, followed by a 2-week rest) and Europe (350 mg/m² every 3 to 4 weeks). The combination trials, of course, will involve varying doses and schedules. To advance the current state of knowledge, future trials should avoid the limitations of the trials detailed here. Specifically, they should include adequate numbers of patients with similar disease histologies and amounts of prior therapy and should employ similar treatment schedules.

References:


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