Irinotecan in Esophageal Cancer

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Irinotecan (Camptosar) has shown activity in several solid tumor malignancies, including gastric and pancreatic cancer. In vitro studies suggest antitumor activity in esophageal cancer cell lines. Sequence-dependent synergy

Introduction

Esophageal carcinoma is an aggressive cancer with a poor prognosis. In 2000, an estimated 12,300 Americans will be diagnosed with this tumor, with approximately 12,100 deaths.[1] Traditionally, patients with localized esophageal cancer, treated with either surgery alone or radiation therapy alone, have had a 5-year survival rate of 5% to 10%.[2,3] More recently, in large phase III trials, patients treated with combined-modality therapy or surgery alone have had 5-year survival rates of 25% to 27%.[4,5]

Despite this improvement in overall survival, most patients with locally advanced disease will have a recurrence. These patients and those presenting with metastatic disease require palliative chemotherapy. These disappointing results have stimulated the search for more aggressive multimodality therapy with more effective chemotherapeutic agents in the treatment of esophageal cancer.

Irinotecan

Irinotecan (Camptosar) has a novel mechanism of action. Once it is converted to its active metabolite SN-38, irinotecan binds to the topoisomerase I-DNA cleavable complex, stabilizes this cleavable complex, and inhibits reannealing of the parent DNA.[6-8] These single-strand breaks are converted to irreversible double-strand breaks when a DNA replication fork encounters a cleavable complex. This process halts the synthesis of nucleic acid in the cell, leading to cell death.[7,8]

Preclinical and Clinical Studies

Ikeda et al examined the antitumor activity of four camptothecin analogs, including SN-38, against six human esophageal cancer cell lines.[9] The authors noted significant antitumor activity for all four camptothecin analogs. In addition, all the cell lines expressed high levels of topoisomerase I, the target of these camptothecin compounds.

Only a small number of patients with esophageal cancer have been treated with single-agent irinotecan. Hecht et al reported their results in 13 patients with previously treated esophageal adenocarcinoma. Of seven evaluable patients treated with weekly irinotecan at 125 mg/m², they noted one complete response and five patients with stable disease.[10]

At the Dana-Farber Cancer Institute, a more recent trial of single-agent irinotecan this time for previously untreated, advanced adenocarcinoma of the esophagus and stomach found an objective response rate of 15% among 34 evaluable patients.[11] Another recent study of the drug in 21 patients with advanced adenocarcinoma of the gastroesophageal junction showed a 14% response rate.[12] In both of these phase II trials, irinotecan was administered at a dosage of 125 mg/m² in cycles of 4 weeks of treatment followed by 2 weeks of rest.

Combination of Irinotecan and Cisplatin

Cisplatin (Platinol) forms the backbone of many combination regimens used today. Toxicities
associated with cisplatin, including neurologic and renal effects, do not overlap with those of irinotecan, which makes this combination attractive. Furthermore, cisplatin acts differently from irinotecan by forming displacement reactions, in which platinum forms a stable bond with DNA, RNA, or other proteins.[13] Intrastrand binding causes kinking of the DNA helix and is associated with limited unwinding. This process disrupts the local structure of DNA and appears to inhibit a number of enzymes important to the cell, leading to apoptosis and cell death.

Cisplatin and irinotecan have demonstrated sequence-dependent synergy in a variety of cancer cell lines in vitro. Kano et al showed that simultaneous administration of irinotecan or SN-38 with cisplatin produced synergistic cytotoxicity in a human T-cell leukemia cell line.[14] Peak synergy was achieved in a human squamous cell carcinoma cell line when cisplatin was given immediately prior to or in combination with SN-38.[15] Sequences in which SN-38 was given prior to cisplatin showed no statistical synergy.

The mechanism of synergy between cisplatin and irinotecan remains unclear at this time. A number of theories based on interesting laboratory findings have been advanced. As quantified by a DNA alkaline elution technique, Masumoto et al found that SN-38 has no effect on the uptake of cisplatin or on the rate of formation of cisplatin-induced DNA interstrand cross-links.[16] Instead, SN-38 appears to reduce the rate of removal of these cross-links. These results were confirmed by Fukuda et al.[17] Cells treated with SN-38 in addition to cisplatin eluted greater amounts of intrastrand cross-linked DNA. This increase persisted at 24 and 48 hours after cisplatin washout, suggesting interference with a DNA repair protein that removes cisplatin-induced DNA adducts.

Fukuda et al also demonstrated a second possible mode of synergy for these two agents.[17] Their experiments suggested that cisplatin increases SN-38 inhibition of topoisomerase I. Nuclear extracts from cells treated with both agents showed decreased quantities of relaxed, uncoiled DNA when compared with untreated cells or cells treated with SN-38 alone. Based on evidence obtained from x-ray diffraction, the authors speculated that severe distortion or kinking of the DNA double helix, caused by intrastrand cisplatin cross-links, might modulate the stabilization of the topoisomerase I-drug-DNA cleavable complex.

Recently, similar results were reported in the ABC-1 lung cancer cell line by Aoe et al.[18] On median-effect plot analysis and combination-index isobologram, synergism was observed when cisplatin was given prior to SN-38. Using a supercoiled-DNA relaxation assay, these authors noted decreased activity of topoisomerase I for 2 to 4 hours after administration of cisplatin and postulated that down-regulation of topoisomerase I by cisplatin contributed to the synergistic effect of these two drugs.

Early Clinical Studies

In Japan, phase I and II trials have evaluated the combination of irinotecan and cisplatin for many solid tumor malignancies, especially non-small-cell lung cancer. These studies typically administered irinotecan (30 to 100 mg/m²) on days 1, 8, and 15, followed by a 1-week rest period, and cisplatin (60 to 80 mg/m²) on day 1 of each treatment cycle. Responses in patients with previously untreated non-small-cell lung cancer ranged from 43% to 54%.[19-22]

Based on these preclinical and clinical findings, Saltz et al initiated a phase I study of weekly irinotecan and cisplatin for advanced solid tumor malignancies at Memorial Sloan-Kettering Cancer Center (MSKCC).[23] This schedule was developed to maximize the opportunity for synergy between the two agents.

Patients received cisplatin over 30 minutes (immediately followed by irinotecan over 90 minutes) weekly for 4 weeks on days 1, 8, 15, and 22. One cycle was defined as 4 weekly treatments, followed by a 2-week rest period. For previously untreated patients, the maximum tolerated doses were 30 mg/m² for cisplatin and 65 mg/m² for irinotecan. Encouraging antitumor activity was noted, including a partial response lasting 5 months in a patient with a gastroesophageal junction tumor. Neutropenia was the main dose-limiting toxicity, and other toxic effects were minimal.

Phase II Trial of Weekly Cisplatin and Irinotecan
In a follow-up study at MSKCC, we initiated a phase II trial of weekly cisplatin 30 mg/m\(^2\) and irinotecan 65 mg/m\(^2\) for unresectable, locally recurrent, or metastatic esophageal adenocarcinoma or squamous cell carcinoma.[24,25] Patients with a performance status of at least 60% and no prior chemotherapy or radiotherapy had adequate renal, hematologic, and hepatobiliary function. For patients with cancer of the gastroesophageal junction, there was at least 50% involvement of the esophagus. Serial dysphagia and quality-of-life assessments were also made at regular intervals.

Of 38 patients entered in the study to date, 35 are evaluable for response and toxicity. Two poorly differentiated cancers were found to have neuroendocrine features on follow-up biopsy, and one gastroesophageal junction cancer appeared to be a gastric cancer on follow-up endoscopy. Accrual continues for patients with squamous cell carcinoma. As outlined in Table 1, patients were typically middle-aged men with an excellent performance status. Almost all patients had metastatic, bidimensionally measurable disease, with involvement of the lymph nodes in 80%, liver metastases in 50%, and lung nodules in 20%. Two-thirds of patients had adenocarcinoma and one-third had squamous cell carcinoma.

As described in Table 2, the major response rate for all patients was 57%, including 2 complete responses (6%), 1 in each histology, and 18 partial responses (51%). Most major responders required only one cycle of chemotherapy to reach a partial response. A significant number of minor responses were also recorded (7 patients, 20%). Few patients failed to benefit from this therapy; only one patient had outright progression of disease. Similar response rates were seen with adenocarcinoma (12 of 23 patients, 52%) and squamous cell carcinoma (8 of 12 patients, 66%). The median duration of response was 4.2 months (range: 1.0 to 8.8 months), and the median actuarial survival was 14.6 months (range: 1.0 to 15.2 months).

Of 20 patients with evaluable dysphagia at baseline, 18 (90%) noted either improvement or resolution of dysphagia with chemotherapy. Significant improvements in overall quality of life, as measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ-C30), and Functional Assessment of Cancer Therapy-General (FACT-G), were noted. Specifically, FACT-G emotional well-being scores as well as EORTC pain, emotional, and work-related functioning scores improved from baseline in responders.

The toxicity profile of the weekly combination of cisplatin and irinotecan is listed in Table 3. Grade 4 neutropenia was seen in 9% of patients. Grade 3 toxic effects included neutropenia (37%), diarrhea (11%), nausea (6%), and fatigue (3%). Six patients (17%) were hospitalized for toxicity, most commonly for neutropenic fever. There were no treatment-related deaths. Delay in treatment occurred at some point during therapy in 23 patients (66%), and attenuation of the dose was required in 7 patients (20%). Overall, 96% of planned treatments were given.

To a certain extent, these findings are being confirmed by Ajani et al at the M. D. Anderson Cancer Center.[26] These investigators are employing the same weekly regimen of cisplatin and irinotecan for gastric and gastroesophageal junction cancers. The preliminary major response rate was 51% in 25 evaluable patients. Similar to the study previously described, gastroesophageal junction cancer accounts for a substantial number of cases in this trial. Neutropenia and diarrhea were again the dominant toxic effects. One of these authors has suggested that perhaps a modification of the schedule to a 2-week-on, 1-week-off cycle might reduce the neutropenia, which typically arises in the third week (J.A. Ajani, personal communication, 1999).

**Ongoing and Future Studies of Combination Regimens**

With the promising phase II results of our weekly cisplatin-irinotecan combination, it was logical to add another antitumor agent to this regimen to improve the response further, and paclitaxel (Taxol) was an obvious choice. Paclitaxel is active in many solid tumors, and in combination with cisplatin, it is considered standard therapy for ovarian, lung, and head and neck cancers.

The mechanism of synergy between paclitaxel and cisplatin is not clear. Jekunen et al found that paclitaxel, at a concentration at which it demonstrates synergy with cisplatin, is capable of altering...
microtubular morphology but not capable of causing arrest of the cell cycle.[27] Even less is known about the combination of irinotecan and paclitaxel. There appears to be no cross resistance between these two antitumor agents,[28] yet antagonism has been reported in an ovarian cancer cell line.[29]

Dosing considerations are critical when combining three chemotherapeutic agents. A weekly 1-hour regimen of paclitaxel and cisplatin has never been evaluated, yet a weekly 3-hour regimen of paclitaxel and cisplatin was tested in a phase I study of patients with solid tumors.[30] The maximum tolerated dose was 30 mg/m$^2$ of cisplatin and 65 mg/m$^2$ of paclitaxel in chemotherapy-naive patients. Neutropenia was the main dose-limiting toxic effect.

Gollerkeri et al studied escalating doses of weekly irinotecan and a 1-hour regimen of paclitaxel in patients with advanced solid tumors.[31] The maximum tolerated dose was 50 mg/m$^2$ of irinotecan and 75 mg/m$^2$ of paclitaxel, with neutropenia as the dose-limiting toxic effect.

Citardi et al demonstrated that a 24-hour regimen of paclitaxel followed by a 30-minute regimen of cisplatin had a greater antitumor effect than a 30-minute regimen of cisplatin followed by a 24-hour regimen of paclitaxel or concurrent cisplatin and paclitaxel in murine leukemia cells.[32] In patients with solid tumors, Rowinsky et al found that the occurrence of neutropenia was significantly greater when cisplatin preceded paclitaxel than in the reverse order.[33]

Based on these data, we initiated a phase I study of a combined weekly 1-hour regimen of paclitaxel, cisplatin, and irinotecan for previously untreated solid tumors. The starting doses and sequence follow: first paclitaxel at 40 mg/m$^2$, then cisplatin at 30 mg/m$^2$, followed by irinotecan at 50 mg/m$^2$. At this level, one patient had a dose-limiting toxic effect in the form of nausea. Expansion of the study to six patients at this dose level is near completion.

Using a similar rationale, we will soon test the combination of irinotecan, cisplatin, and fluorouracil (5-FU) for solid-tumor malignancies. Again, 5-FU has broad activity in a variety of solid tumors and has shown synergy with both cisplatin[34] and irinotecan in vitro.[14] A phase I study to combine cisplatin, irinotecan, and concurrent radiation therapy for locally advanced esophageal cancer is also planned. Irinotecan has been shown to be a radiation sensitizer in vitro[35] and in vivo.[36] In combination with cisplatin and radiation, irinotecan has shown activity in a phase I/II adjuvant non-small-cell lung cancer study in Japan.[37]

**Conclusion**

The combination of weekly cisplatin and irinotecan is active in the treatment of previously untreated, advanced esophageal carcinoma. This regimen has similar activity for both adenocarcinoma and squamous cell carcinoma. Therapy was well tolerated. Toxicity appears to be limited mostly to grade 3 neutropenia and grade 2/3 diarrhea. Significant relief of dysphagia was noted by almost all patients with symptoms at baseline. Quality-of-life indices showed improvement in responding patients. Further exploration of this combination and schedule (or modified schedule as Ajani has suggested) is warranted for other solid-tumor malignancies. This couplet forms an ideal base for the addition of other chemotherapeutic agents (ie, paclitaxel or 5-FU) or the addition of radiation therapy for locally advanced disease.

**References:**


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