Irinotecan (CPT-11): Recent Developments and Future Directions–Colorectal Cancer and Beyond

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ABSTRACT

Since its approval in the United States in 1996, irinotecan (CPT-11, Camptosar®, Pharmacia Corp.; Peapack, NJ) has undergone extensive clinical evaluation. In the past five years, the focus of development has evolved from evaluation of single-agent activity in refractory disease settings to evaluation of front-line irinotecan-based combination chemotherapy regimens and integration of irinotecan into combined modality regimens. Important studies have been performed clarifying the role of irinotecan in treating colorectal and other gastrointestinal cancers, small cell and non-small cell lung cancer, and a variety of other malignancies. Preclinical studies performed in conjunction with these clinical trials have also provided significant insights into the pharmacology, metabolism, mechanisms of resistance, and molecular determinants of response. This review summarizes that progress, focusing on the achievements of the past five years. The Oncologist 2001;6:66-80

INTRODUCTION

Five years ago, irinotecan was granted accelerated approval by the FDA for use in the treatment of recurrent, metastatic colorectal cancer. Since then, a great deal has been learned about its pharmacology, metabolism, mechanisms of toxicity, and spectrum of clinical activity. This review summarizes the progress that has been made in the laboratory and in the clinic during that period.

PRECLINICAL DEVELOPMENTS

Pharmacology and Metabolism

Irinotecan is converted to its active metabolite, SN-38, by carboxylesterase. Careful analysis of carboxylesterase activity in normal human tissues demonstrated highest levels of enzyme activity in the liver followed by duodenum, jejunum, ileum, colon, and rectum [1]. Tumor tissue obtained from the colon and liver tended to have lower levels of SN-38 formation than matched normal colon and liver tissue, respectively, and this correlated with lower levels of carboxylesterase activity [1, 2]. Although it is likely that conversion of irinotecan within the liver and gastrointestinal tract are the most important determinants of tumor exposure to SN-38, even low levels of local conversion of irinotecan to SN-38 within the tumor may be important since, unlike the liver, tumors have no way of detoxifying SN-38 through glucuronidation. As a result, the SN-38 generated within the tumor may also contribute to the cytotoxicity of irinotecan [2]. This observation provides the theoretical basis for oral administration of irinotecan because this would take advantage of the first-pass metabolism effect, potentially resulting in enhanced generation of SN-38 within the liver and liver metastases. Preclinically, attempts have been made to transfer carboxylesterase cDNA into tumors to enhance local production of SN-38 [3, 4].

Substantial variability in topoisomerase (topo) activity has been observed by Guichard and colleagues, who
observed a 76% coefficient of variation in normal tissue and a 79% coefficient of variation in tumor tissue [2]. Overall, topo I activity was approximately 50% higher in colon tumors than in normal colon tissue, while it was approximately 50% lower in liver metastases than in normal liver tissue. Topo I activity also appeared to be inversely correlated with extent of disease, with lower levels found in primary tumors obtained from patients diagnosed with Dukes’ C colon cancer than in those diagnosed with Dukes’ A colon cancer. This suggests that topo I activity may be downregulated during the process of tumor invasion and metastasis. Clinical trials are under way to examine these features prospectively in patients treated with irinotecan.

New insights have been gained regarding the metabolic activation and detoxification of irinotecan. The primary route of metabolism for irinotecan is through P450 CYP3A4, which generates the inactive metabolites APC and NPC. Once tissue carboxylesterase transforms irinotecan to SN-38, the major mechanism of detoxification is through glucuronidation by UGT1A1 of the hepatic uridine diphosphate glucuronosyltransferase (UDP-GT) [5] system. Gupta and colleagues demonstrated that rats pretreated with an inhibitor of this enzyme, such as valproic acid, experienced 99% inhibition of SN-38G formation and a 270% increase in the SN-38 area under the concentration-time curve (AUC) [6]. It has also been observed that individuals with Gilbert’s syndrome (a congenital deficiency of UGT1A1 activity found in up to 6% of the population) have a similar reduction in detoxification of SN-38 to SN-38G and experience much greater toxicity when given standard doses of irinotecan [7]. The lack of complete correlation between inhibition of UDP-GT activity and change in SN-38 pharmacokinetics may be due to variable expression and activity of cellular transporter pumps within the biliary tract, including the p-glycoprotein (pgp) and the canalicular multispecific organic anion transporter (cMOAT) proteins [8]. Pretreatment with cyclosporine, which inhibits pgp and cMOAT pump function, results in significant increases in irinotecan, SN-38 and SN-38G plasma AUCs [9].

Combination and Sequential Therapy

When topo I inhibitors are used in conjunction with topo II inhibitors, preclinical models suggest an important and sequence-specific interaction. Exposure of cells to a topo I inhibitor must precede exposure to a topo II inhibitor, or therapeutic antagonism may result. This interaction is believed, at least in part, to be due to downregulation of topo I and compensatory upregulation of topo II that occurs soon after administration of a topo I inhibitor. As a result, the direct cytotoxic effect of the topo I inhibitor is coupled with the enhanced cytotoxic effect of the topo II inhibitor, producing increased cytotoxicity. Results of preclinical studies designed to evaluate this phenomenon show substantial variability. Some have confirmed the hypothesis of significant sequence specificity for the combined use of topo I and topo II inhibitors [10]; however, others have not [11]. This variability may be related to the specific topo inhibitors and cell lines used as well as the drug concentrations and durations of exposure used in the experiments.

The combination of irinotecan and 5-fluorouracil (5-FU) has received considerable attention due to the clinical relevance of this combination in the treatment of colorectal and other gastrointestinal malignancies. The results have also been inconsistent, although the majority report additivity or synergy when irinotecan precedes 5-FU [12-14]. However, other sequences and even simultaneous exposure to irinotecan and 5-FU have been reported to generate additive or synergistic effects, as well [12, 15, 16]. Here, too, differences probably relate to varying concentration and duration of drug exposure, particular model system employed, and interval between drug exposures. The cellular basis for this interaction may include a build-up of S-phase fraction cells when irinotecan is administered prior to 5-FU, which may enhance 5-FU cytotoxicity. Pharmacokinetic behavior does not seem to be substantially altered for either drug whether administered simultaneously or in sequence. Some have reported that irinotecan reduces expression of thymidylate synthase, thereby supporting the sequence of irinotecan → 5-FU [17], but this finding has not been consistent in other model systems [13]. Introducing uracil into DNA may induce new topo cleavage sites, suggesting that the opposite sequence may be more advantageous [18]. Irinotecan does not appear to modulate protein expression of dihydropyrimidine dehydrogenase or folypolyglutamate synthetase, nor does there appear to be any change in cleavable complex formation by prior exposure to 5-FU [13]. Several investigators have found relationships between thymidylate synthase (TS) expression and sensitivity to 5-FU [19] and cleavable complex formation and sensitivity to topo I inhibitors [20]. Pavillard and colleagues noted an inverse relationship between TS activity and cleavable complex formation. These data suggest that the cytotoxic effects of irinotecan and 5-FU are largely independent of each other at the molecular level and the interactions observed may largely be due to cell cycle distribution and to factors that determine the intrinsic sensitivity of cells to each drug independently—TS expression for 5-FU and cleavable complex formation for irinotecan. From a clinical perspective, this may mean that it is more important to integrate both drugs into a coordinated therapeutic plan than to administer the drugs simultaneously on any particular schedule.

The combination of irinotecan and cisplatin has received a great deal of attention because both target DNA and each
works in a mechanism quite distinct from the other. In addition, these drugs have somewhat overlapping patterns of activity while having little overlapping toxicity. However, insight into the mechanism of this interaction remains limited. No pharmacologic interaction occurs between these drugs [21].

Mechanisms of Resistance

A number of mechanisms of resistance to irinotecan have been identified in preclinical models. These include decreased topo I levels due to post-translational or post-transcriptional changes or gene rearrangement [22-25], topo I mutations that affect cleavable complex formation, decreased topo I catalytic activity, decreased binding of the camptothecin to topo I [26], reduced expression of carboxylesterase [27], and increased efflux of irinotecan out of the cell [28, 29] that may involve pgp (for irinotecan) and multidrug resistance proteins (for SN-38) [29]. Little data are available on the relative contribution and frequency of these events in patients who progress on treatment with irinotecan.

DIARRHEA: MECHANISMS AND PREVENTION

Diarrhea and myelosuppression remain the most clinically significant and common toxicities of irinotecan. The diarrhea appears to be primarily secretory, but may also have some exudative components [30]. This mixed pathophysiology may be one reason why late diarrhea associated with irinotecan is so difficult to prevent. Early recognition of diarrhea and initiation of loperamide at the first signs of diarrhea have significantly reduced the incidence of grade 4 diarrhea from 24% to 9% and improved the clinical tolerability of irinotecan. The mechanism by which loperamide reduces irinotecan-induced diarrhea is not well established but probably involves its inhibitory effect on smooth muscle tone that leads to prolongation of intestinal transit and increased time for fluid absorption [31]. Nevertheless, more than 80% of patients develop some grade of diarrhea following treatment with irinotecan. The median time to onset of delayed diarrhea is five days following high-dose, once-every-three-week dosing and 11 days (i.e., three days after the second dose) in the weekly dosing regimen [32, 33].

Interleukin 15 (IL-15) is a cytokine found in intestinal crypt cells that promotes modest proliferation of intestinal epithelial cells [34]. When administered repetitively before and during irinotecan, IL-15 reduced the incidence of diarrhea from 93% to 8% and treatment-related mortality from 86% to 0% in Fisher 344 rats [35]. Morphologically, IL-15 appeared to prevent the shortening and destruction of duodenal microvilli, the shortening of the colon crypts, and the reduction in the number of colonic goblet cells [35]. The molecular mechanism behind this protective effect of IL-15 is unknown but may involve inhibiting chemotherapy-induced apoptosis of intestinal cells, directly stimulating intestinal cell growth or altering the number or function of intestinal lymphocytes or other immunomodulatory cytokines, including interferon-γ. JBT-3002, a synthetic lipopeptide, induces monocyte-derived cytokines, including IL-15, in the lamina propria of the intestinal mucosa of mice [36]. Oral administration of JBT-3002 effectively protected mice from lethal diarrhea induced by high-dose irinotecan. Morphologically, JBT-3002 induced IL-15 expression in tissue macrophages located in the lamina propria of the ileum, and prevented the inflammatory cell infiltration and shortening of microvilli that occurs in the ileum following irinotecan treatment in mice. Importantly, pretreatment with JBT-3002 did not protect CT-26 murine colon carcinoma cells from the cytotoxic effects of irinotecan in vitro.

If local luminal concentrations of SN-38 cause or contribute to the delayed diarrhea, administering antibiotics prior to irinotecan could alter gut flora so that less β-glucuronidase is produced and back conversion of SN-38G to SN-38 in the gut is reduced [37]. Traditional Japanese medicines, known as Kampo medicines, such as TJ-14, TJ-114, and baicalin, contain natural glucuronides that effectively inhibit β-glucuronidase production in the gut but have not been effective clinically in preventing irinotecan-induced late diarrhea [38].

Thromboxane A₂ stimulates chloride ion secretion and decreases water absorption in the gut, thereby resulting in diarrhea. This pathway has been implicated in animal models of irinotecan-induced diarrhea; however, plasma levels of prostaglandin E₂ (a related prostaglandin more easily measured than A₂) were normal in one study of patients with irinotecan-induced delayed diarrhea [30]. Drugs that inhibit thromboxane A₂ production (such as cyclooxygenase inhibitors) or receptor binding of thromboxane A₂ could, theoretically, reduce irinotecan-induced diarrhea. Clinical evaluation of COX-2 inhibitors in this setting is attractive not only for the possibility of toxicity reduction, but also because inhibition of COX-2 may also promote cancer cell apoptosis and potentially increase the antitumor effectiveness of irinotecan and other cytotoxic drugs. Diets supplemented with 3% or 6% fish oil appeared to protect the intestinal mucosa of tumor-bearing nude mice from the morphological changes induced by irinotecan without abrogating its antitumor effects. This may be mediated through the same thromboxane A₂ pathway [39].

Acetorphan, an enkephalinase inhibitor with antisecretory properties, has been used alone and combined with loperamide for treating late diarrhea [30]. A small phase II trial suggested that combining acetorphan and loperamide was more effective than acetorphan alone at reducing the incidence and duration of grade 3-4 diarrhea [30].


**Clinical Progress**

**Colorectal Cancer**

The largest body of data and longest clinical experience with irinotecan have been in patients with advanced colorectal cancer. The most significant development in this area in the last five years has been that several important phase III trials have confirmed and expanded initial observations of clinical activity reported from phase II trials.

**Recurrent and Refractory Disease**

In recurrent or refractory colorectal cancer, phase II trials conducted from 1993-1997 documented response rates from 11% to 22%. Response duration (6-9 months) and survival (8-10 months) were consistent across trials, regardless of treatment schedule used. These data left two important questions unresolved. First, was treatment with irinotecan better than the best supportive care alone (the standard of care in the United Kingdom and the Netherlands), and second, was treatment with irinotecan better than infusional 5-FU (a popular second-line treatment option in the U.S. and many parts of Europe)? Two complementary phase III studies were designed to address those questions. In the first, patients with metastatic colorectal cancer having documented progression on one to two prior 5-FU-based regimens and within six months of last treatment with 5-FU were randomized in a 2:1 fashion to single-agent irinotecan 350 mg/m² (or 300 mg/m² if age ≥70 or WHO performance status = 2) administered once every three weeks plus best supportive care (BSC) or to BSC alone [40]. Two hundred seventy-nine patients were randomized: 189 to receive irinotecan + BSC and 90 to receive BSC alone. Because one arm of this study did not require antitumor therapy, response rates were not assessed or reported. Median survival was 9.2 months in the irinotecan + BSC arm versus 6.5 months in the BSC alone arm (Log-rank p = 0.0001). One-year survival rates of 36% versus 14%, respectively, translated into a 2.6-fold survival advantage for irinotecan-treated patients. Using the European Organization for the Research and Treatment of Cancer Quality-of-Life Questionnaire-C30 (EORTC QLQ-C30) quality-of-life (QOL) assessment tool, the overall QOL for those patients treated with irinotecan was significantly better than those patients who received BSC alone. In a companion phase III study, 267 patients with metastatic colorectal cancer and progressive disease following one prior 5-FU-based regimen were randomized to treatment with irinotecan 300-350 mg/m² once every three weeks or to one of three infusional 5-FU regimens: the de Gramont regimen (which consists of a two-hour infusion of leucovorin, followed by a bolus injection of 5-FU, followed by a 22-h infusion of 5-FU, repeated days 1 and 2, administered in two-week cycles); continuous infusion 5-FU, with no scheduled breaks; and weekly 24-h 5-FU infusions, with or without leucovorin, for six consecutive weeks, followed by a two-week break [32]. Patients were randomized on a 1:1 basis. The median survival of those patients treated with irinotecan was 10.8 months compared with 8.5 months for those treated with infusional 5-FU (log rank p = 0.035). Probability of survival at one year was 45% for irinotecan-treated patients versus 32% for 5-FU-treated patients. Overall, the EORTC QLQ-30 QOL instrument did not detect any differences in QOL between those patients treated with a 5-FU infusion and those treated with irinotecan. The data from these two trials demonstrating prolonged survival and comparable or improved QOL established irinotecan as the treatment of choice in patients who are medically fit to receive chemotherapy who have colorectal cancer that has progressed or recurred following 5-FU treatment.

<table>
<thead>
<tr>
<th>Author</th>
<th>Irinotecan dose (mg/m²)</th>
<th>5-FU dose (mg/m²)</th>
<th>LV dose (mg/m²)</th>
<th>n</th>
<th>Pts</th>
<th>Response rate</th>
<th>Median progression-free survival (mo)</th>
<th>Median overall survival (mo)</th>
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<td>425 qd × 5</td>
<td>20 qd × 5</td>
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<td>4.3a</td>
<td>12.6c</td>
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<tr>
<td></td>
<td>125 q wk × 4</td>
<td>500 q wk × 4</td>
<td>20 q wk × 4</td>
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<td>39%</td>
<td>7.0b</td>
<td>14.8e</td>
<td></td>
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<tr>
<td></td>
<td>125 q wk × 4</td>
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<td>-</td>
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<td>200 q 2 wk</td>
<td>187</td>
<td>22%</td>
<td>4.4c</td>
<td>14.1f</td>
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<tr>
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<td>-</td>
<td>2,300 CIV × 24 h q wk × 6</td>
<td>500 q wk × 6</td>
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<tr>
<td></td>
<td>180 q 2 wks</td>
<td>400 bolus over 22 h q 2 wk</td>
<td>200 q 2 wk</td>
<td>198</td>
<td>35%</td>
<td>6.7c</td>
<td>17.4f</td>
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</table>

\[p < 0.001; ^a p = 0.004; ^b p = 0.041; ^c p = 0.005; ^d p < 0.001; ^e p = 0.031\]
First-Line Chemotherapy

Phase II trials performed in the mid-1990s also demonstrated single-agent activity for irinotecan when used in the front-line treatment of patients with advanced colorectal cancer, yielding response rates of 19%-32%, median response duration of response 7.6-9.1 months, and median survival of 11.8-12.1 months. Given the clinical non-cross-resistance of irinotecan and 5-FU, a coordinated effort was made to explore the combined use of these agents as front-line treatment for patients with advanced metastatic colorectal cancer. Two phase III trials were performed comparing 5-FU + leucovorin combinations with CPT-11, 5-FU + leucovorin (IFL) regimens (Table 1). In a study conducted in the U.S., Canada, and Australia, a weekly schedule of irinotecan and bolus 5-FU/leucovorin was compared with a reference arm of 5-FU and leucovorin administered on a daily × 5 schedule (Mayo Clinic regimen) [41]. A third arm, not included in the comparative analysis, was single-agent irinotecan administered on a weekly schedule. Median progression-free survival was 7.0 months for the IFL arm, 4.3 months for the 5-FU/LV arm (p ≤ .004, log-rank) and 4.2 months for single-agent irinotecan. In addition, patients treated with irinotecan/5-FU/leucovorin had a higher confirmed response rate than the group treated with 5-FU + leucovorin (39% versus 21%, p < .001, Chi-square). The group treated with the three-drug regimen had a median overall survival of 14.8 months compared with 12.6 months for the group treated with 5-FU + leucovorin (p = .04, log-rank). In an exploratory regression analysis, patients with favorable prognostic factors (consisting of a baseline performance status of 0 or a normal baseline lactic dehydrogenase) appeared to derive the greatest benefit from the three-drug IFL regimen [42]. Global QOL scores were comparable among all three arms of the study and were well maintained for the duration of treatment. Toxicity profiles were consistent with previous observations for all three treatment arms. Patients treated with IFL had a higher rate of grade 3-4 diarrhea (22.7% versus 13.2%) and grade 3-4 vomiting (9.7% versus 4.1%) than those treated with the daily × 5 regimen of 5-FU and leucovorin. Patients treated with 5-FU + leucovorin had higher rates of grade 3-4 mucositis, grade 4 neutropenia, and febrile neutropenia than the other two groups.

The European study evaluated 385 patients treated with 5-FU/leucovorin by one of two infusional regimens ± irinotecan [43]. The confirmed response rate for the IFL arm was significantly higher than that of the 5-FU + leucovorin arm, 35% versus 22% (p = .005, Chi-square). In addition, patients treated with the irinotecan/5-FU/leucovorin combination had significantly longer progression-free survival (6.7 versus 4.4 months, p < .001, log-rank) and overall survival (17.4 versus 14.1 months, p = .031, log-rank) than those who received 5-FU + leucovorin as front-line therapy for metastatic colorectal cancer. Interestingly, only 34% of patients treated with front-line 5-FU + leucovorin in the European study received subsequent treatment with irinotecan compared with 56% of patients on the U.S./Canadian/Australian study. Consistent with the U.S./Canadian/Australian study, global QOL was similar for both arms and well-maintained throughout treatment. The time to performance status deterioration was longer in the irinotecan treatment group than in the control group (11.2 versus 9.9 months, p = .046, log-rank). More patients treated with the irinotecan-containing regimens experienced grade 3-4 diarrhea (22% versus 10%) and grade 3-4 neutropenia (42% versus 11%). Demonstration of a significant survival advantage in two large phase III studies has led to the adoption of irinotecan, 5-FU, and leucovorin as a new treatment standard for first-line therapy in patients with metastatic colorectal cancer.

The next logical step in the development of irinotecan has already begun. Three trials have been initiated evaluating these irinotecan/5-FU/leucovorin regimens as adjuvant chemotherapy in patients with locally advanced colon cancer. In the U.S., intergroup study C89803 is randomizing 1,260 patients with stage III colon cancer to a 30-week course of treatment with the irinotecan/5-FU/leucovorin regimen used in the prior U.S./Canadian/Australian study or to a 32-week course of treatment with a reference adjuvant regimen consisting of weekly 5-FU + leucovorin (Roswell Park regimen). The primary endpoint of this trial is disease-free survival with secondary endpoints of overall survival and correlation of outcome with baseline molecular characterization of the tumor, including thymidylate synthase, p53, p27, vascular endothelial growth factor, microvessel count, detection of the deleted in colon cancer gene, microsatellite instability, and topo I expression. In conjunction with Aventis, the Gastrointestinal Cancer Committee of EORTC is conducting a phase III trial (EORTC 40993: PETACC-3) that will administer a six-month course of similar regimens tested in the advanced stage study to treat 1,794 patients with predominantly stage III colon cancer. A third study will evaluate the impact of irinotecan when added to 5-FU and leucovorin in a smaller cohort of 400 patients with high-risk stage III colorectal cancer. The primary endpoint for all three studies is relapse-free survival. Accrual is under way in all three studies, and they are expected to complete accrual in 2002.

Molecular characterization of colorectal cancers has not only yielded important insights into the pathogenesis of colorectal cancer but, more recently, into the possible basis for the clinical sensitivity or resistance of gastrointestinal tumors to 5-FU-based chemotherapy. Several groups have reported that colon, rectal, and gastric cancers with high levels of thymidylate synthase expression are less likely to respond to
5-FU-based therapy (5-FU alone or in combination with leucovorin) than tumors with lower levels of TS expression [44]. The most plausible explanation for this observation is that clinically achievable concentrations of intracellular 5-FU were insufficient to effectively block TS function in cells with high levels of TS expression. Although methodology of TS assessment and cut-off points used to define “high” and “low” levels of expression have differed from study to study, this observation may provide the theoretical basis for the prospective evaluation of gastrointestinal tumors for TS expression and selection of therapy based on this result. With the availability of drugs such as irinotecan and oxaliplatin that are active against colorectal cancer and exert their cytotoxic effects independently of TS, this hypothesis can now be evaluated in a properly designed, prospective clinical trial.

Esophageal and Gastric Cancers

Irinotecan is associated with an 18%-33% response rate when used as a single agent in patients with advanced gastric cancer [45, 46, 99]. This makes irinotecan one of the more active single agents for this disease. Given the consistent demonstration of additivity/synergy between irinotecan and cisplatin in preclinical model systems, this combination has been explored in the treatment of patients with advanced gastric cancer (Table 2). Boku and colleagues treated 44 metastatic gastric cancer patients with irinotecan 70 mg/m²/day 1 and 15 and cisplatin 80 mg/m²/day 1 only with cycles repeated every four weeks [47]. He observed a 48% response rate in a mixed group of patients, with 59% of those who had received no prior therapy responding to the irinotecan + cisplatin combination. The most common side effects of this regimen were grade 4 neutropenia (57% of patients), grade 3-4 diarrhea (20% of patients), and grade 3 nausea (18% of patients).

Because potentially beneficial interactions occur only when both drugs are administered on the same day, some investigators have explored an alternative dosing schedule for the irinotecan + cisplatin combination in which both drugs are given on the same day. Using this concurrent treatment regimen, Ajani and colleagues reported an objective response rate of 55% in previously untreated patients and 50% in previously treated patients with gastric cancer [49, 50]. The authors recommended further pursuit of this combination regimen, but with an abbreviated two-week-on/one-week-off schedule and/or a lowering of the dose of cisplatin to improve tolerability. Preliminary results suggest that this regimen is similarly effective in patients with esophageal carcinoma, and that these patients may tolerate these doses a bit better than patients with gastric cancer [49]. Ilson and colleagues reported the results of a phase II trial in which 35 patients with metastatic or unresectable esophageal cancer were treated with cisplatin 30 mg/m² followed by irinotecan 65 mg/m² on a weekly × 4 basis, followed by a two-week rest [52]. The objective response rate to this regimen was 57%. In the subset of patients experiencing dysphagia at the time of entry onto study, 90% experienced improvement or complete resolution of this symptom. Onset of relief occurred after a median of one cycle of therapy. Prospective QOL evaluation performed in conjunction with this study revealed significant reduction in pain and improvement in overall QOL that correlated with objective shrinkage of tumors. Therapy was well-tolerated, with grade 4 neutropenia occurring in only 9% of patients. Other toxicities included grade 3 anemia (31%), grade 3 diarrhea (11%), and grade 3 vomiting (3%). No patient experienced grade 4 diarrhea or vomiting. Ongoing clinical trials in esophageal and gastric cancer include combination chemotherapy regimens combining irinotecan with 5-
FU, cisplatin, paclitaxel, or docetaxel. Combined modality regimens under development for esophageal cancer include irinotecan ± cisplatin and irradiation in patients with locally advanced disease.

**Pancreatic Cancer**

Two single-agent phase II studies published in the mid-1990s reported objective response rates for irinotecan of 9% and 11% in patients with advanced, previously untreated adenocarcinoma of the pancreas. Building on this, Rocha-Lima evaluated a regimen combining gemcitabine with irinotecan on a weekly × 3, q four-week basis and observed objective responses in two of three patients with previously untreated pancreatic cancer in a phase I trial [53]. Forty-five patients with chemotherapy-naïve, locally advanced, or metastatic pancreatic cancer were treated with this combination in a phase II trial. Nine patients experienced an objective response (RR = 20%). Median time to treatment failure was 2.9 months, and median survival was 6.0 months [54]. Based on these results, a phase III trial has been initiated to compare the irinotecan + gemcitabine combination to a reference standard of single-agent gemcitabine in patients with newly diagnosed advanced-stage adenocarcinoma of the pancreas. Another ongoing phase II trial is evaluating the irinotecan + docetaxel combination.

**Non-Small Cell Lung Cancer (NSCLC)**

As front-line therapy for patients with advanced stage NSCLC, single-agent response rates for irinotecan have ranged from 13% to 36%. For previously treated patients, the response rate has been much lower (0%-10%). For many of the same reasons cited above, irinotecan + cisplatin has been the first and most extensively studied irinotecan-based regimen in this disease (Table 3). A variety of schedules have been used. Masuda and colleagues treated 69 patients with stage IIIB and IV NSCLC with irinotecan 60 mg/m² on days 1, 8, and 15 and cisplatin 80 mg/m² on day 1 every four weeks [55]. A 52% response rate was observed in the 64 patients evaluable for response. Median survival was 10.2 months (11.3 months for stage IIIB and 8.8 months for stage IV). The most common toxicities included grade 4 neutropenia (38% of patients), grade 3-4 anemia (35%), grade 3-4 nausea/vomiting (35%), and grade 3-4 diarrhea (19%). Only 52% of patients were able to receive all three scheduled doses of irinotecan during the first cycle of therapy. Based on these promising results, this regimen was evaluated in a three-arm phase III trial against a cisplatin + vindesine regimen (cisplatin 80 mg/m² day 1 and vindesine 3 mg/m² days 1, 8, and 15) and single agent irinotecan (100 mg/m² days 1, 8, 15) in 398 patients with stage IIIB-IV NSCLC [56]. The primary endpoint was overall survival. The objective response rate was highest in the cisplatin + irinotecan arm (43%) versus 31% for cisplatin + vindesine and 21% for irinotecan alone (p < .001). Median survival, however, did not differ among the three arms: 11.6 months versus 10.9 months versus 10.6 months, respectively. In a subset analysis restricted to only those patients with stage IV NSCLC, median survival for the irinotecan + cisplatin group appeared to be superior to that in the other two groups (12.4 months versus 8.7 months versus 9.7 months). Similar results were obtained in a two-arm phase III trial conducted in Japan in which the irinotecan + cisplatin regimen was compared to a standard cisplatin + vindesine control arm [57]. DeVore and colleagues performed a multicenter phase II trial in the U.S. using the same doses and schedules of irinotecan and cisplatin [58]. The objective response rate was 29%, and median survival was 9.9 months. Consistent with the Japanese experience, dose reductions were required frequently for this regimen with 60% of

<table>
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<tr>
<th>Investigator</th>
<th>Regimen mg/m² (unless noted)</th>
<th>n Pts</th>
<th>Response rate</th>
<th>Median overall survival (mo)</th>
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<tr>
<td>Oshita [61]</td>
<td>Irinotecan 60 d 1-3 + etoposide 60 d 1-3 + G-CSF 50 µg/m²/d 4-17</td>
<td>59</td>
<td>22%</td>
<td>10.0</td>
</tr>
<tr>
<td>Masuda [56]</td>
<td>Cisplatin 80 d 1 + irinotecan d 1, 8, 15</td>
<td>398</td>
<td>43%</td>
<td>11.6</td>
</tr>
<tr>
<td></td>
<td>Cisplatin 80 mg/m² d 1 + vindesine 3 d 1, 8, 15</td>
<td></td>
<td>31%</td>
<td>10.9</td>
</tr>
<tr>
<td></td>
<td>Irinotecan 100 d 1, 8, 15</td>
<td></td>
<td>21%</td>
<td>10.6</td>
</tr>
<tr>
<td>Niho [57]</td>
<td>Cisplatin 80 d 1 + irinotecan 60 d 1, 8, 15 q 4 wks</td>
<td>210</td>
<td>29%</td>
<td>10.5</td>
</tr>
<tr>
<td></td>
<td>Cisplatin 80 d 1 + vindesine 3 d 1, 8, 15 q 4 wks</td>
<td></td>
<td>22%</td>
<td>11.4</td>
</tr>
</tbody>
</table>
patients requiring dose reductions of irinotecan to below 40 mg/m^2 at some point in their treatment. A follow-up study was performed using an alternative dosing regimen for cisplatin in which lower doses (30 mg/m^2) were administered on a weekly \times 4 basis along with irinotecan 65 mg/m^2 [59]. In that study, the overall response rate was 42% with a median survival of 11.6 months. Importantly, the incidence of grade 3-4 neutropenia was 26% (compared with 46.1% for the monthly cisplatin regimen), febrile neutropenia was 4% (compared with 11.5% for the monthly cisplatin regimen), and the doses of irinotecan could be better maintained on the weekly schedule with a relative dose intensity of 89%.

The combination of weekly irinotecan + cisplatin also appears promising as salvage treatment of NSCLC. In 21 patients with advanced NSCLC that was unresponsive to previous platinum-based chemotherapy, Nakanishi and colleagues reported a 29% objective response rate and a median survival of 7.4 months [62]. Seventy-six percent of patients required some dose modification or omission during the first two cycles of therapy, suggesting that these patients are less tolerant of this regimen than chemotherapy-naive patients. Other regimens under evaluation in phase I and II clinical trials in patients with advanced NSCLC include irinotecan + carboplatin, paclitaxel, docetaxel, gemcitabine, and UFT.

Irinotecan is an effective radiosensitizing drug in vitro and in vivo [63]. Exposure of mice to noncytotoxic doses of irinotecan 1 h prior to treatment with ionizing radiation resulted in significant tumor regression compared with the use of CPT-11 or radiation treatment alone. The combination was highly synergistic against the MS-1 small cell lung cancer and LX-1 mixed small cell/non-small cell human tumor xenografts. Several phase I/II clinical trials have now been performed using combined modality treatment with irinotecan + irradiation, primarily in patients with locally advanced NSCLC [64] (Table 4). Response rates of 60%-80% have been achieved using this combination by several independent groups [65-71]. Multicenter phase II trials are under way to evaluate this strategy further.

### Small Cell Lung Cancer (SCLC)

As a single agent, irinotecan is associated with a 16%-47% response rate in patients with relapsed or refractory SCLC [96-98]. The irinotecan + cisplatin combination has been evaluated in chemotherapy-naive as well as previously treated patients (Table 5). In chemotherapy-naive patients, the combination of cisplatin 60 mg/m^2 on day 1 and irinotecan 60 mg/m^2 on days 1, 8, and 15, repeated every 28 days is associated with an overall response rate of 84% [72]. It is important to note that this response rate was as high in patients with extensive-stage disease (86%) as it was for patients with limited-stage disease (83%). Median survival for extensive-disease patients was impressive at 13.0 months. Irinotecan + carboplatin appears equally effective, with objective responses observed in 75% of patients [73]. Irinotecan + etoposide was associated with a 66% response rate 12-month median survival in 50 patients with extensive-stage SCLC [74]. More intensive doses of this combination, or the addition of a third drug to this regimen, can result in higher objective response rates but require the use of hematopoietic growth factors and may not result in improved survival rates. Results have recently emerged from a phase III trial for patients with chemotherapy-naive SCLC in which they were randomized to the cisplatin + irinotecan regimen described above or to a reference control arm of cisplatin 80 mg/m^2 day 1 and etoposide 100 mg/m^2 days 1-3 repeated every three weeks [75]. One hundred fifty-eight patients were randomized between the two arms. Median time to treatment failure was 6.9 months for those treated with irinotecan + cisplatin (CP) and 4.8 months for those treated with etoposide + cisplatin (EP).

#### Table 4. Phase I/II data on irinotecan + XRT in locally advanced NSCLC

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Phase</th>
<th>Regimen mg/m^2</th>
<th>Response rate</th>
<th>Median overall survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chakravarthy [66]</td>
<td>I</td>
<td>Irinotecan 30-50 q wk \times 6 RT 40 Gy thoracic concurrent + 20 Gy boost to tumor</td>
<td>58%</td>
<td>TE</td>
</tr>
<tr>
<td>Yamada [67]</td>
<td>I</td>
<td>Irinotecan 30-60 q wk \times 4 + carboplatin 20 q wk \times 4 RT 60 Gy in 2 Gy fractions q wk \times 6</td>
<td>60%</td>
<td>TE</td>
</tr>
<tr>
<td>Fukuda [68]</td>
<td>I</td>
<td>Irinotecan 40-60 d 1, 8, 15 q 28 d + cisplatin 60-80 d 1 q 28 d RT 24 Gy in 2 Gy fractions/d (Cycle 1) and 26-36 Gy in 2 Gy fractions/d (Cycle 2)</td>
<td>65%</td>
<td>N/A</td>
</tr>
<tr>
<td>Takeda [65]</td>
<td>I/II</td>
<td>Irinotecan 30-40 q wk \times 6 RT 60 Gy (2 Gy \times 30) concurrently</td>
<td>77%</td>
<td>15.7</td>
</tr>
<tr>
<td>Saka [69]</td>
<td>II</td>
<td>Irinotecan 60 q wk \times 6 RT 60 Gy (2 Gy \times 30) concurrently</td>
<td>79%</td>
<td>N/A</td>
</tr>
<tr>
<td>Yokoyama [70]</td>
<td>I/II</td>
<td>Irinotecan 40-60 d 1, 8, 15 + cisplatin 60-80 d 1 RT 60 Gy (2 Gy \times 30) concurrently</td>
<td>67%</td>
<td>10.4</td>
</tr>
</tbody>
</table>

TE = too early
Irinotecan Update

Importantly, median survival was also superior for those who received irinotecan + cisplatin (12.8 versus 9.4 months, \( p = .0021 \), one-sided log-rank test). Grade 3-4 neutropenia was more common on the EP arm while grade 3-4 nausea, vomiting, and diarrhea were more common on the CP arm. These encouraging findings have resulted in the initiation of a confirmatory phase III trial in the U.S. Irinotecan-based regimens have also demonstrated activity as second-line therapy for patients with relapsed or refractory SCLC. In a phase II trial of irinotecan, etoposide, and G-CSF in patients with SCLC that had recurred following cisplatin-based front-line therapy, objective responses were seen in 14 of 24 patients (71%) [76]. Irinotecan + paclitaxel, with both drugs administered on a weekly basis, was associated with objective responses in 5 of 11 patients in a phase I/II trial in patients with previously treated SCLC [77].

Mesothelioma

Malignant mesothelioma is characteristically unresponsive to chemotherapy, with single-agent response rates usually in the 10%-20% range. Several combination chemotherapy regimens have recently reported response rates in excess of 20%. Cisplatin + irinotecan produced a 27% objective response rate (40% if patients with unidimensional disease are included) in a group of previously treated patients with malignant pleural mesothelioma [79]. In a small subset of patients, pleural concentrations of SN-38 approximated, and in some cases, exceeded, plasma concentrations, suggesting that the malignant tissue could be exposed to therapeutic concentrations of SN-38 even when irinotecan was administered intravenously.

Brain Tumors

Irinotecan has considerable activity against neuroblastoma in vitro and in vivo [80]. In adults, neuroblastoma is an uncommon malignancy. The majority of malignant brain tumors in adults are gliomas: anaplastic astrocytoma, anaplastic oligodendroglioma, or glioblastoma multiforme. Response rates of 5% have been reported for single-agent irinotecan in patients with newly diagnosed, unresectable glioblastoma multiforme (GBM) and 10%-15% in patients with recurrent or refractory GBMs. Toxicity has been remarkably mild [81]. Pharmacokinetic analysis revealed some possible explanations for this [82]. Compared with two previous studies in which irinotecan was administered on the same dose and schedule to patients with advanced colorectal cancer, patients treated on this study had a two-fold higher clearance rate that resulted in an irinotecan AUC of only 40% of those obtained in the other studies. AUCs for SN-38 and SN-38G were only 25% of those achieved in the previous studies. Ninety-one percent of patients treated on this study were receiving concomitant antiepileptic drugs such as phenytoin, carbamazepine, and

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Regimen mg/m² (unless noted)</th>
<th>n Pts</th>
<th>Response rate</th>
<th>Median overall survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kudoh [72]</td>
<td>Irinotecan 60 d 1, 8, 15 + cisplatin 60 d 1</td>
<td>40</td>
<td>30%</td>
<td>84%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35</td>
<td>28%</td>
<td>86%</td>
</tr>
<tr>
<td>Suguira [73]</td>
<td>Irinotecan 50 d 1, 8, 15 + carboplatin 300 d 1 q 4 wks</td>
<td>13</td>
<td>15%</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>0%</td>
<td>67%</td>
</tr>
<tr>
<td>Sekine [78]</td>
<td>Irinotecan 20-100 q wk + cisplatin 25 q wk × 9 + etoposide 60 d 1-3 q wks 1, 3, 5, 7, 9</td>
<td>10</td>
<td>20%</td>
<td>100%</td>
</tr>
<tr>
<td>Nakamura [74]</td>
<td>Irinotecan 60 IV d 1, 8, 15 + etoposide 80 d 2-4</td>
<td>0</td>
<td>50</td>
<td>10%</td>
</tr>
<tr>
<td>Noda [75]</td>
<td>Irinotecan 60 d 1, 8, 15 + cisplatin 60 d 1 q 4 wks</td>
<td>77</td>
<td>2.7%</td>
<td>83.1%</td>
</tr>
<tr>
<td></td>
<td>Etoposide 100 d 1-3 + cisplatin 80 d 1 q 3 wks</td>
<td>77</td>
<td>9.1%</td>
<td>67.5%</td>
</tr>
<tr>
<td><strong>Second-line therapy</strong></td>
<td>Sensitive</td>
<td>20</td>
<td>10%</td>
<td>71%</td>
</tr>
<tr>
<td></td>
<td>Refractory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Masuda [76]</td>
<td>Irinotecan 70 d 1, 8, 15 + etoposide 80 d 1-3 + G-CSF</td>
<td>9</td>
<td>7</td>
<td>0%</td>
</tr>
<tr>
<td>Okihrio [71]</td>
<td>Irinotecan 60 + cisplatin 60 d 1, 8, 15</td>
<td>11</td>
<td>36%</td>
<td>45%</td>
</tr>
</tbody>
</table>

\( p = .0021 \) (one-sided log-rank); ED = extensive stage; LD = limited stage; NA = not available
phenobarbital, compared with none of the patients on the colorectal cancer trials. This suggests a drug-drug interaction between the antiepileptic medications and irinotecan. The most likely explanation is that the antiepileptic medications caused an induction in the P450 CYP3A4 enzyme. This enzyme is responsible for converting irinotecan to APC and NPC, two inactive metabolites, before irinotecan could be converted to SN-38. A follow-up study has confirmed that the AUC of APC for patients receiving phenobarbital was increased 2.6-fold over AUCs obtained in patients who were not taking phenobarbital [83]. Induction of CYP3A4 could explain the higher rate of clearance, the lower AUCs of SN-38 and SN-38G, and the reduced rate of severe toxicity observed in these trials. Given these findings, the clinical activity of irinotecan may have been underestimated in patients with malignant gliomas. Follow-up trials to determine the maximum tolerated dose and pharmacologic behavior of irinotecan in this group of patients have been initiated, and doses as high as 800 mg/m² have been administered on a once-every-three-week basis [84, 85]. Clinical and pharmacokinetic data from those trials are pending.

**Cervical Cancer**

Early reports from Japan suggested that irinotecan was quite active as first- or second-line therapy of women with squamous cell carcinoma of the cervix [86]. Follow-up trials in the U.S. yielded conflicting results. One trial performed in 14 women with platinum-resistant cervical cancer reported no objective responses and poor tolerance of weekly irinotecan [87]. Three other trials of single-agent irinotecan have yielded response rates of 13%-21% [88-90]. Although these three studies were also performed in patients with recurrent disease, they did not require patients to be platinum-resistant. This suggests that progression on platinum is associated with clinical cross-resistance to single-agent irinotecan, a pattern somewhat similar to that observed in NSCLC trials. Prior pelvic irradiation appears to predispose cervical cancer patients to an increased risk of gastrointestinal toxicity, and the majority of such patients required dose reductions. More recently, lower doses of irinotecan have been used in conjunction with cisplatin as neoadjuvant therapy for women with locally advanced cervical carcinoma [91]. In a previously untreated group of patients, 18 of 23 (78%) achieved a radiographic objective response. Although surgery was performed in 9 of 10 patients with stage IB or IIB disease and in 5 of 10 patients with stage IIIIB disease, no information on pathologic response, disease-free, or overall survival is available. This regimen was relatively well-tolerated, with grade 3-4 diarrhea occurring in only 10% of treatment cycles and grade 4 neutropenia occurring in only 19% of treatment cycles. Further exploration of lower doses of irinotecan, used in combination with cisplatin or radiation, are under way in patients with locally advanced cervical cancer (neoadjuvant therapy) and advanced-stage disease (salvage therapy).

**Ovarian Cancer**

Single-agent irinotecan has promising activity in the treatment of adenocarcinoma of the ovary, with response rates of 16%-30% reported in small phase II trials in patients with recurrent disease [86]. The combination of irinotecan + cisplatin has been tested in patients with refractory or recurrent ovarian cancer [92]. Despite the fact that 84% of patients had platinum-resistant disease (i.e., did not respond to or relapsed within six months of receiving a platinum-based regimen), 10 of 25 patients (40%) responded to this second-line regimen of irinotecan + cisplatin. Treatment was relatively well-tolerated, and median survival was 12 months. In another study involving a mixed group of patients with platinum-sensitive and platinum-resistant disease, 18 of 30 patients (60%) responded to second-line irinotecan + cisplatin [93]. Interestingly, the response rate did not differ between platinum-resistant and platinum-sensitive patients. All patients underwent surgery to remove recurrent tumor prior to initiation of salvage therapy. In a correlational study, the amount of nuclear protein required for complete DNA relaxation (an indirect measure of topo I activity) was substantially higher in non-responders than responders (p = .02), suggesting lower topo I activity levels in tumors resistant to the irinotecan + cisplatin combination. Correlating topo I expression and activity in clinical trials has been difficult to accomplish and has yielded conflicting results. The correlation observed by Kigawa and colleagues needs to be confirmed in a larger group of patients and should include direct assessment of topo I expression and activity.

**Breast Cancer**

Surprisingly little clinical data exist on the use of irinotecan in this common chemosensitive tumor. There is evidence of preclinical activity for irinotecan against breast cancer cell lines in vitro and human tumor xenografts in vivo [94]. Response rates of 8% and 23% have been reported in two phase II trials [86], but follow-up studies have been lacking. With the advent of many new agents demonstrating activity in this disease, including docetaxel, vinorelbine, Herceptin, and capecitabine, combination phase II trials in patients progressing after standard doxorubicin + cyclophosphamide ± paclitaxel would be of substantial interest.

**Head and Neck Cancer**

A recent phase II trial reported a 21% single-agent response rate in a group of 24 patients with squamous cell
carcinoma of the head and neck who had not received any prior chemotherapy for metastatic disease. The initial dose of 125 mg/m²/week had to be reduced after the initial cohort of patients developed unacceptable gastrointestinal and hematologic side effects. Subsequent patients were treated at a starting dose of 75 mg/m²/week, and dose-escalated to 100 mg/m²/week as tolerated. This approach was associated with a much lower rate of toxicity and appeared to produce a response rate equivalent to that of the group treated at the higher dose level. Future efforts will evaluate irinotecan in combination with other active agents, such as cisplatin, and radiation [95].

CONCLUSIONS AND FUTURE DIRECTIONS

A great deal of progress has been made over the past five years in defining the role of irinotecan in the treatment of patients with colorectal cancer when used as a single agent in the treatment of recurrent colorectal cancer and, more recently, irinotecan used in combination with 5-FU and leucovorin in the front-line treatment of patients with metastatic colon cancer. The logical next step in the development of irinotecan has already been taken: phase III trials of the irinotecan, 5-FU, and leucovorin combination are under way in the adjuvant setting to evaluate the impact of irinotecan on disease-free and overall survival in patients with locally advanced colon cancer.

It would be a mistake, however, to view the activity of irinotecan as limited to one disease. In fact, phase II and III data have emerged that suggest that irinotecan may have an important role in the treatment of a number of other cancers, including SCLC and NSCLC, esophageal cancer, gastric cancer, cervical cancer, malignant brain tumors and ovarian cancer. A phase III trial of this combination versus cisplatin + etoposide in patients with extensive stage SCLC demonstrated a significant survival advantage for the irinotecan + cisplatin treated patients. This trial had one of the longest median survivals ever reported from a phase III trial in extensive stage SCLC. If confirmed in the current trial, this will represent a significant advance in the treatment of this difficult malignancy. Phase III trials conducted in Japan have demonstrated substantial activity of the cisplatin + irinotecan combination as front-line treatment of patients with advanced NSCLC, although a survival advantage was not detected. The high response rate and low toxicity distinguish the irinotecan + cisplatin combination from others currently under development for the treatment of advanced esophageal cancer. These characteristics make it an attractive regimen for phase III evaluation.

Recent experience has demonstrated that concerns over overlapping toxicity patterns between irinotecan and other drugs, especially 5-FU, were unfounded and that full doses of both drugs could be administered safely and effectively. A modification in the schedule of drug administration for the cisplatin + irinotecan combination so that both drugs are administered on a weekly basis appears to preserve, or possibly enhance, the safety and efficacy profile of this combination, especially for patients who are symptomatic from their cancer. Trials are under way to evaluate supportive measures to further reduce the incidence of delayed diarrhea. These include a phase III trial of a long-acting preparation of octreotide, Sandostatin LAR®, in patients receiving single-agent irinotecan. Clinical trials of acetorphan, IL-15 (or agents that induce the production of IL-15), and fish oil supplements containing ω-3 fatty acids are either under way or planned in the near future.

Finally, the quest for molecular determinants of response to irinotecan continues. Despite substantial efforts, the association between topo I expression in tumor tissue and response remains unclear, and inconsistent results have been obtained from clinical trials to date. While procurement of fresh tumor tissue for analysis remains a formidable obstacle, the contribution of other factors identified in preclinical studies, such as cellular localization of the topo I enzyme, localization of the enzyme to an actively replicating portion of DNA, topo I gene mutation, and alterations in the camptothecin binding site on the cleavable complex must be considered and methods developed for their assessment. By learning more about the contribution of these factors to the clinical activity or resistance that is observed, irinotecan could be used as more of a molecularly targeted compound than a non-specific cytotoxic agent.

Clinically, the next five years will see progress on many fronts, including development of better irinotecan-based drug combinations, the development of combined modality treatment involving irinotecan + radiation, the evaluation of irinotecan in the adjuvant and neoadjuvant settings, and the identification of irinotecan’s activity in tumors beyond colorectal cancer. It is only through these efforts that the full therapeutic potential of this important drug will be realized.

ACKNOWLEDGMENTS

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