Topotecan (Hycamtin) is a promising new topoisomerase I-targeting anticancer agent that first entered clinical trials in 1989 under National Cancer Institute sponsorship in collaboration with SmithKline Beecham. In 1996, it

Introduction

Topotecan is a synthetic analog of the naturally occurring parent compound, camptothecin, which was originally derived from the Chinese tree, Camptotheca acuminata.[1-4] Topotecan contains both a C-9 tertiary amine side chain, a C-10 hydroxyl group that enhances its aqueous solubility, and a chiral carbon at C-20 (Figure 1). Like all camptothecin derivatives, the (S)-isomer is much more biologically active than the (R)-isomer.[5] However, unlike the other clinically available camptothecin analog, irinotecan (Camptosar), topotecan is not a prodrug, and in the lactone form it can directly interact with topoisomerase I. An intact closed lactone ring is essential for this activity, but the lactone also makes all camptothecins unstable in aqueous solutions by undergoing a rapid, reversible, pH-dependent, nonenzymatic hydrolysis to form the less active hydroxycarboxylic acid (Figure 1).[6,7] At neutral or basic pH, the equilibrium for this reaction favors the formation of the inactive topotecan carboxylate, while acidic pH favors the stabilization of topotecan in the active lactone form.[8]

Mechanism of Action

DNA topoisomerase I is a 100-kDa monomeric eukaryotic enzyme that relaxes torsionally strained, supercoiled, double-stranded DNA. Topoisomerase I activity is found in all mammalian cells and is potentially involved in DNA-related functions, such as replication,[9] recombination,[10] and RNA transcription.[11] Topoisomerase I preferentially binds to both positively and negatively supercoiled duplex DNA, forming a short-lived catalytic intermediate in which the enzyme is covalently bound to a tyrosine residue at the 3’ end of a single-stranded DNA break. This normally transient intermediate, called the cleavable complex, allows for the relaxation of the torsional strain by facilitating passage of the intact strand through the single-stranded DNA nick, or by rotating around the remaining intact DNA phosphodiester bond. Rapid DNA relegation followed by enzyme dissociation regenerates a torsionally relaxed, intact double helix. Because of the rapidity of this reaction, topoisomerase I covalently bound to DNA in the cleavable complex is not normally detectable. However, in the presence of camptothecins, which inhibit the relegation reaction by binding noncovalently to the topoisomerase I-DNA cleavable complex, these protein-linked, single-strand DNA breaks accumulate within the cell (Figure 2). Not all topoisomerase I cleavage sites are equally stabilized by camptothecins. There is, instead, a preference for guanine residues at the +1 position relative to the single-stranded break.[12-13] The persistence of topotecan-induced single-stranded DNA breaks is not sufficient to cause cell death, because drug removal results in regeneration of intact DNA. However, if a DNA replication fork encounters a topotecan-stabilized cleavable complex, these lesions convert into lethal double-stranded DNA damage (fork collision model; Figure 2).[14,15] This cytotoxic DNA damage in some cell lines can ultimately trigger pathways that lead to DNA degradation patterns consistent with programmed cell death, or apoptosis.[16,17] Because of the need for ongoing DNA synthesis, topotecan is most lethal during the S-phase of the cell cycle.[18] This mechanism of action may have potential clinical consequences because cell-cycle, phase-specific cytotoxic agents typically require longer drug exposure times to maximize cell kill. Consequently, phase I evaluation of a 21-day continuous infusion of topotecan is nearing completion.[19-21] Unlike antimetabolite agents, topotecan is not an enzyme inhibitor in the classic sense, because it does not cause cell death by eliminating the function of an essential enzyme. Instead, topotecan converts an endogenous enzyme, topoisomerase I, into a cellular poison. The presence of
topoisomerase I activity is absolutely essential for drug activity.[22] Higher levels of topoisomerase I have been reported in various human tumors, including leukemic blasts[23] and colon,[24] head and neck,[25] and prostate cancers.[24,26] Because increased topoisomerase I activity can enhance sensitivity to camptothecins,[22,27] a potential selective advantage for killing these tumor cells was predicted for these drugs. However, more recent data have shown a poor correlation between absolute topoisomerase I protein levels and relative camptothecin sensitivity in various cultured cancer cell lines including ovarian, colon, and leukemic.[28-30]

Other factors also contribute to the induction of topotecan-induced cytotoxicity. Yeast mutants with decreased ability to repair double-stranded DNA damage are more sensitive to camptothecins than are wild-type cells,[31] and more efficient repair of DNA double-strand breaks has been proposed as a potential mechanism of camptothecin resistance in human cells.[32] Increased sensitivity to camptothecins by human leukemia cells has been correlated with loss of cell-cycle regulation and G2 checkpoint control.[33] The relationships between camptothecin-induced cell death, cell-cycle regulation, DNA-repair, and the induction of apoptosis are currently being studied.[34]

**Mechanisms of Resistance**

Although various mechanisms of topotecan resistance have been characterized in vitro, little is currently known about the mechanisms of clinical drug resistance. Cell lines with decreased topoisomerase I activity[34,35] or mutations in the topoisomerase I enzyme that preserve catalytic activity but diminish interactions with camptothecins[36-43] have demonstrated camptothecin resistance in laboratory experiments. Reduced intracellular drug accumulation may also contribute to drug resistance,[44,45] although the mechanisms of topotecan transport and retention within the cell have not been well characterized. The role of the P-glycoprotein-mediated, multidrug resistant (MDR) efflux pump in topotecan resistance is also undefined. Cultured cell lines that over express P-glycoprotein have less ability to accumulate intracellular drug and are about ninefold more resistant to topotecan.[46-48] However, this degree of resistance is much less than the 200-fold decrease in sensitivity seen with classic MDR substrates, such as doxorubicin or vinblastine.[46]

Hence, the relevance of these observations to the treatment of tumors that highly express MDR, such as colon cancer, must still be determined.

**Mutagenicity**

Camptothecin derivatives, such as topotecan, can cause chromosomal aberrations, including increased sister-chromatid exchanges, gene deletions, and gene rearrangements.[49]

Topoisomerase II inhibitors, such as doxorubicin and etoposide, which are known to increase the risk of secondary malignancies, such as acute myelogenous leukemia, cause similar patterns of DNA damage.[50] The carcinogenic risk following topotecan therapy is unknown; however, the theoretical risk, which topotecan shares with other highly useful anticancer agents, should not deter its use in appropriate clinical settings. Nonetheless, following topotecan therapy, patients should be carefully monitored for adverse drug effects, particularly those patients with the potential for prolonged survival.

**Radiation Sensitization**

Topotecan may also be useful as a radiation sensitizer. Low concentrations of topotecan can enhance radiation lethality in laboratory experiments,[51] and clinical trials are currently evaluating topotecan in combination with radiation therapy for several tumor types, including those in the lung and central nervous system.[52]

**Phase I Studies: Schedules, Doses, and Toxicity**

Topotecan has been most commonly administered at the FDA-approved dose of 1.5 mg/m²/d infused daily over 30 minutes for 5 consecutive days every 3 weeks.[53-55] In hematologic malignancies, a 5-day continuous infusion at 2.0 mg/m²/d every 3 weeks has also been used.[23,56,57] Other schedules of administration evaluated in phase I trials include a single infusion every 3 weeks[58] and continuous infusions for 24 hours,[59-61] 72 hours,[56,62] and 21 days.[19] Oral[63] and intraperitoneal[64] topotecan administration has also been examined.

The most common toxicity of topotecan is myelosuppression, especially neutropenia, which is the dose-limiting effect of most schedules tested. Anemia and thrombocytopenia are less common; however, they may occur more frequently when topotecan is administered on weekly and 21-day infusion schedules.[19] Although topotecan-induced myelotoxicity is not cumulative,[65] heavily pretreated patients may be at increased risk for more severe cytopenias.[54] In one phase I study,
use of granulocyte-colony-stimulating factor (G-CSF [Neupogen]) did not allow further dose escalation because of development of dose-limiting thrombocytopenia and fatigue.[54] Higher doses, however, up to 3.5 mg/m²/d, were administered in a second trial with G-CSF support.[66] In preliminary results, when these higher, more toxic doses were given to patients with colorectal cancer, no substantial improvement in antitumor activity was noted. [E. K. Rowinsky, MD, personal communication, 1996]

**Myelosuppression**

Phase I studies of topotecan, like several other recently approved anticancer agents, have commonly used an aggressive definition of dose-limiting toxicity, allowing for up to 5 days of severe neutropenia (absolute granulocyte counts ≤ 500 mm³) before ceasing dose escalation.[53] Consequently, in 452 previously treated advanced ovarian cancer patients who were administered 1.5 mg/m²/d of topotecan, neutrophil nadirs less than 500/mm³ were extremely frequent, occurring in 81%.[67] Granulocyte counts were lowest on day 11 with recovery typical by day 22.[67] Thrombocytopenia was less common, but platelet counts under 25,000/mm³ did occur in 26% of patients and severe anemia with a hemoglobin of less than 8 g/dL occurred in 40%.[67] The clinical consequences of this myelosuppression were substantial, with the combined incidence of fever, sepsis, or infection associated with severe neutropenia in 26%. Whether this severe degree of topotecan-induced myelosuppression in previously treated ovarian cancer patients is necessary for optimal antitumor activity is unknown.

In 112 pretreated patients with advanced ovarian cancer, about 25% received G-CSF in courses subsequent to cycle one, and the overall toxic death rate was 1.8%.[67] Given this frequency of severe myelosuppression, it would seem prudent to require patients to have an absolute granulocyte count of 1,500/mm³ and a platelet count of 100,000/mm³ before initiating topotecan chemotherapy.[67] Routine use of prophylactic G-CSF is not generally recommended.[68,69] In the event of severe neutropenia, reducing the dose of topotecan by 0.25 mg/m² in subsequent cycles of therapy should be considered. Full dosage can be resumed following recovery from toxicity with a normalization of blood count. Alternatively, beginning the use of G-CSF may be considered on day 6 of each subsequent cycle, at least 24 hours after the last dose of topotecan. Granulocyte colony-stimulating factor should not be administered concurrently with topotecan therapy. However, whether the use of G-CSF to maintain topotecan dose intensity will improve disease control is unknown. Therefore, it is not currently possible to make definitive recommendations regarding the proper use of colony-stimulating factors with topotecan therapy. Thus, for patients experiencing severe topotecan-induced neutropenia, subsequent chemotherapy cycles may be administered at reduced doses, or, alternatively, G-CSF may be added in an attempt to maintain dose intensity.

**Other Nonhematologic Toxicities**

Additional nonhematologic toxicities commonly associated with topotecan therapy include nausea and vomiting, alopecia, mucositis, elevated liver transaminases, skin rash, and fever.[53,54] Most of these side effects are mild and do not require alterations in the treatment plan. In phase I studies of leukemia patients, the dose-limiting toxicity of topotecan was mucositis[23,57] and when topotecan was administered orally for 21 consecutive days, the major dose-limiting toxicity was severe diarrhea.[63] This diarrhea, which generally begins after 2 weeks of therapy, resembles the severe gastrointestinal toxicity seen with the other clinically approved camptothecin derivative, irinotecan.[4] Because prolonged (21-day) intravenous administration of topotecan is not generally associated with severe diarrhea, this toxicity probably occurs as a local effect of orally administered drug on the gastrointestinal mucosa.[63] Preliminary studies with oral topotecan given once daily for 10 days have demonstrated better tolerability.[70]

**Clinical Pharmacology**

Following short IV infusions, topotecan lactone is rapidly cleared from plasma by nonenzymatic hydrolysis to form the less active carboxylate. Both species circulate in human plasma with an area-under-the-concentration-vs-time-curve (AUC) ratio of lactone to total topotecan (lactone plus carboxylate) of 28%, (range, 18% to 33%) (Table 1).[53-55,58,65] Topotecan demonstrates linear pharmacokinetics, with a terminal plasma half-life of topotecan lactone of 2.5 hours (range, 1.7 to 3.4 hours) and a total drug half-life of 3.6 hours (range, 2.9 to 4.3 hours).

The kinetics of topotecan lactone may be complicated by hydrolysis of the lactone ring prior to intravenous infusion. Detailed analyses by Grochow et al demonstrated that intravenous preparations of topotecan in 5% dextrose (pH 4.5) resulted in hydrolysis of as much as 16% of the
drug with a half-life of 30 minutes.[53-65] Even greater hydrolysis may occur when topotecan is administered in normal saline, which has a higher pH than dextrose.[71] The clinical consequences of this preinfusion hydrolysis are not known.

Elimination of topotecan carboxylate occurs principally via the kidneys, and about 36% (range 30% to 40%) of total drug intake can be recovered unchanged from the urine following a short, 30-minute intravenous infusion (Table 1). During infusions longer than 24 to 72 hours, 50.6% to 67.5% of topotecan can be recovered in the urine.[61,72] Excretion of topotecan into the bile was demonstrated in one patient who had biliary topotecan concentrations that were 1.5-fold greater than those in the plasma.[58] No active plasma metabolites of topotecan have been identified. In studies of orally administered topotecan, bioavailability ranged from 32% to 44%.[73-74] Unlike most other camptothecin analogs, topotecan plasma protein binding is low, less than 20%.[61,75] In laboratory studies, topotecan has virtually no interaction with human serum albumin.[76] This lack of protein binding may contribute to topotecan's ability to penetrate the central nervous system. For children, cerebrospinal fluid (CSF) concentrations of topotecan lactone were 32% of simultaneous plasma concentrations.[77] This observation may prove clinically important because topotecan has activity in diseases that frequently involve the central nervous system, such as small-cell lung cancer and hematologic malignancies.

Pharmacodynamic correlations between parameters of systemic topotecan exposure and drug effects have been observed inconsistently. Topotecan plasma concentrations and/or AUCs were predictive of the degree of drug-induced myelosuppression in most,[23,53,59,60,65,72,78] but not all,[19,61] studies.

### Dose Adjustments for Abnormal Renal and Hepatic Function

Preliminary guidelines have been proposed for the use of topotecan in patients with abnormal renal and hepatic function.[79,80] Based on studies of 14 patients with abnormal renal function, topotecan therapy was not recommended for those with creatinine clearances \( \leq 20 \text{ mL/min} \).[79] Dose reductions of 50% to 0.75 mg/m\(^2\)/d were recommended for patients having creatinine clearances ranging from 20 to 39 mL/min, with additional dose reductions to 0.5 mg/m\(^2\)/d for those who had been heavily pretreated. No alteration in topotecan dosing was considered necessary for patients with creatinine clearances \( \geq 40 \text{ mL/min} \). Note that these guidelines incorporate the same risk of grade 4 neutropenia as that described for standard dosing of patients with normal renal function. Thus, caution should be used, and further dose reductions for those who tolerate severe neutropenia poorly may be warranted.

In 21 patients with hepatic dysfunction defined by serum total bilirubin levels more than 1.2 mg/dL (range, 1.4 to 14.9 mg/dL), no alteration in topotecan pharmacokinetics and no increase in toxicity was observed.[80] Hence, no adjustment in topotecan dosing was recommended for patients with abnormal liver function. However, only three patients with total bilirubin levels greater than 3.0 mg/dL received the recommended dose of topotecan of 1.5 mg/m\(^2\)/d, and thus, some caution should be used in extrapolating these findings to the larger population. Interestingly, these three patients were given 12 courses at 1.5 mg/m\(^2\) and had no episodes of febrile or severe neutropenia. In contrast, six patients with normal liver function in this study (five of whom were heavily pretreated) received standard dose topotecan and developed grade 4 neutropenia in 23 of 46 courses—an incidence which is similar to that reported in other phase II studies.[67] If these preliminary findings of decreased neutropenia are confirmed in a larger number of patients with hepatic injury, potential explanations include decreased enterohepatic circulation of topotecan, or the presence of an as yet unidentified active hepatic metabolite that may contribute to topotecan's toxicity.[80]

### Antitumor Activity

#### Ovarian Cancer

FDA approval of topotecan for previously treated patients with advanced ovarian cancer was based on a phase III randomized trial.[67,81] Patients were assigned to either topotecan, 1.5 mg/m\(^2\)/d for 5 days, or paclitaxel, 175 mg/m\(^2\) infused over 3 hours, with both treatments repeated every 3 weeks. The response rate on the topotecan arm was 21% (95% confidence interval [CI], 13% to 28%), which was at least equivalent to the paclitaxel response rate of 15% (95% CI, 7% to 19%; \( P = .092 \)).[81]

The median time to documented radiologic response was significantly longer on topotecan therapy than on paclitaxel therapy (9 vs 6 weeks; \( P = .002 \)).[81] However, because only one prior platinum-based regimen was allowed, this population included patients who were still potentially sensitive to retreatment with platinum chemotherapy.
Furthermore, the two treatment arms were not equally intense with regard to toxicity since much greater myelosuppression occurred on the topotecan arm. Febrile neutropenia was observed in 23% of patients receiving topotecan, compared to less than 3% of those receiving paclitaxel. Topotecan also produced substantially more grade 4 thrombocytopenia than paclitaxel (Taxol), 25.3% vs 1.8% of patients, respectively, and much more grade 3 or 4 anemia, 40.5% vs 6.3%, respectively.[67] Nonetheless, these observations do confirm other reports of topotecan's activity in ovarian cancer.[82-84]

The extent of prior platinum-based therapy alters the rates of response to subsequent topotecan therapy. In a large trial of topotecan in advanced ovarian cancer, 111 patients were stratified according to their response history to cisplatin (Platinol) chemotherapy.[84] The response rates were highest, 26.7% (95% CI, 12.3% to 45.9%) in the cisplatin-sensitive patients, defined as those who had initially responded to but later relapsed more than 6 months after discontinuing their initial cisplatin-based chemotherapy. Such patients frequently respond to retreatment with additional platinum-based chemotherapy.

In contrast, the response rate was poorest—only 5.9% (95% CI: 0.7% to 19.7%)—in patients who had previously progressed or who demonstrated only stable disease during their initial cisplatin chemotherapy. Thus, little topotecan activity was demonstrated in those who were truly refractory to platinum-based therapy. They are the patients for whom new and better treatments are urgently needed. Although ovarian cancer is very responsive to initial treatment with platinum-based chemotherapy, most patients still die from their disease. Whether topotecan, with its novel mechanism of action, will ultimately provide more meaningful clinical benefit in ovarian cancer will be determined by ongoing trials evaluating its use in combination chemotherapy in newly diagnosed patients.

**Lung Cancer**

Topotecan is an active agent in small-cell lung cancer.[85-87] Forty-eight untreated extensive-stage small-cell lung cancer patients were administered topotecan on a daily for 5 days schedule, at a dose of 2.0 mg/m²/d, which is higher than the FDA-approved dose.[85] A window-of-opportunity design permitted evaluation of topotecan activity in untreated patients, but limited the number of courses they could receive. Patients who had a partial response to topotecan after 4 cycles, stable disease after 2 cycles, or progressive disease at anytime were crossed over to standard chemotherapy (with cisplatin and etoposide [Vepesid]). The response rate to topotecan prior to crossover was 39% (95% CI, 25% to 53%) with a median response duration of 4.8 months (95% CI, 3.0 to 7.5 months).[85] Of 17 patients who had no response to topotecan, 4 subsequently responded to cisplatin and etoposide therapy. Topotecan-induced myelosuppression was considerable. Even with routine administration of G-CSF, 29% of patients experienced grade 3 or 4 neutropenia. Grade 3 or 4 thrombocytopenia was observed in 38%.

Other phase II studies of topotecan in small-cell lung cancer at the approved dose of 1.5 mg/m² reported response rates ranging from 10% to 33%.[86,88] (Table 2). As with ovarian cancer, a patient's prior response history may be an important determinant of subsequent response to topotecan therapy. Small-cell lung cancer patients who are refractory to initial front-line chemotherapy appear to have lower response rates when treated with topotecan (Table 2).[88] SmithKline Beecham is currently conducting a randomized phase III trial comparing topotecan use vs conventional chemotherapy with cyclophosphamide (Cytoxan, Neosar), doxorubicin, and vincristine in a more favorable group of small-cell lung cancer patients who progress more than 3 months after initial therapy with etoposide and cisplatin. Another NCI-sponsored phase III trial is examining the value of adding topotecan to standard therapy with etoposide and cisplatin in previously untreated extensive-stage small-cell lung cancer patients. Following four cycles of etoposide and cisplatin, patients are randomized to observation or to four additional cycles of topotecan. These studies should better define the value of topotecan in the treatment of small-cell lung cancer. In non-small-cell lung cancer, topotecan appears to be less active with response rates ranging from 0% to 15% in untreated patients.[71,89,90] However, in a subset analysis from one study of untreated non-small-cell lung cancer patients, partial responses were observed in 5 of 14 patients with squamous carcinoma of the lung.[90] Additional testing of topotecan in this specific histologic type of lung cancer is ongoing.

**Hematologic Malignancies**

In a study of 22 patients with myelodysplastic syndromes and 25 patients with chronic myelomonocytic leukemia (CMML), topotecan was administered at a dose of 2 mg/m² over 24 hours for 5 days as a continuous infusion.[91] Complete responses were achieved in 27% and 28% of patients, respectively, with an overall median remission duration of 7.5 months. Remarkably, eight
patients with karyotype abnormalities who subsequently attained complete responses became cytogenetically normal while in remission. Hematologic improvement was also observed in 6 of the 47 patients entered in this trial. The toxicity of this regimen was high, with 17% of patients dying from myelosuppression-associated complications and 19% experiencing grade 3 or 4 mucositis. Whether lower, less toxic doses are as active is unknown. Nonetheless, because single-agent studies of other drugs, such as cytarabine, produce overall remission rates in myelodysplasia of only 10% to 20%,[92] these results are very encouraging and additional studies are planned.

Recent studies also suggest that topotecan has activity in acute leukemia. In a phase I study of continuous infusions of topotecan at 0.7 to 3.5 mg/m²/d for 5 days every 3 to 4 weeks, three complete and two partial responses were observed in 27 refractory or relapsed acute leukemia patients, for an overall response rate of 18%.[57] Responses occurred in patients with acute myelocytic leukemia (AML) and acute undifferentiated leukemia. One of three patients with chronic myelocytic leukemia (CML) in blast phase also responded. At the recommended dose of 2 mg/m²/d, 1 of 12 patients had severe mucositis and 5 had mild to moderate mucositis; however, other toxicities were minimal.

In a second phase I trial of 17 patients with acute leukemia, a phase II dose of 2.1 mg/m²/d was recommended, and a comparable response and toxicity profile was observed.[23] In this study, one complete response occurred in a patient with CML in blast crisis and one partial response was seen in a patient with AML, for an overall response rate of 12%. Significant reductions in circulating blast-cell numbers occurred in all courses, and transient complete clearance of leukemic blasts from peripheral blood was described in 11 courses.

In a novel pharmacokinetically guided phase I trial of acute childhood leukemia, the amount of topotecan administered was escalated so as to define the precise amount of drug exposure corresponding to the dose-limiting toxicity.[93] For a 5-day continuous infusion of topotecan, the maximum-tolerated systemic exposure (MTSE) paralleled the steady-state plasma concentration of 4.0 ng/mL (9.5 nM).[93] In 18 total patients, 1 complete and 1 partial response was recorded, occurring in patients with Burkitt’s lymphoma and with B-cell ALL, respectively. The peripheral blast count cleared completely in six patients; however, progressive disease usually occurred before or soon after the scheduled time for retreatment.

In chronic lymphocytic leukemia (CLL), a disease in which the majority of malignant cells are not actively dividing, no response was seen in 12 patients.[94] In contrast, preliminary data from a trial in previously treated patients with non-Hodgkin’s lymphoma, topotecan demonstrated response rates of 32% (95% CI, 19% to 68%); Table 2).[95,96] Further trials of topotecan combined with other agents active in hematologic malignancies, such as cytarabine and etoposide are ongoing.[97]

Other Tumors
Promising preliminary activity has also been seen in pediatric malignancies, such as neuroblastoma[98] and rhabdomyosarcoma (Table 2).[99] A recent phase II study in 32 untreated pediatric patients with disseminated neuroblastoma was recently published in preliminary form.[98] Using an upfront phase II window design, 63 untreated patients were randomized to either two courses of topotecan at 2 mg/m²/d for 5 days or to paclitaxel at 350 mg/m² over 24 hours. In the 32 patients randomized to topotecan, a response rate of 37% was observed compared with 16% for the 31 patients on the paclitaxel arm. If minor responses after two cycles are also included, the combined overall response rate was 66% for the topotecan patients and 19% for the paclitaxel arm. In colorectal cancer, topotecan appears to be less active than irinotecan, with reported response rates ranging from 0% to 10%, whether the drug is given daily for 5 days,[100,101] by 21-day continuous infusion,[20] or at a higher dose of 3.5 mg/m²/d with G-CSF (Table 2). [E. K. Rowinsky, MD, personal communication, March, 1997] Phase II results in other solid tumors are summarized in Table 2.[102-114]

**Topotecan by 21-Day Infusion**

Because of the preclinical rationale that prolonged drug exposures may improve activity and increase cell kill, a prolonged 21 day topotecan infusion regimen has been developed.[19] The recommended phase II dose on this schedule is 0.53 mg/m²/d, with myelosuppression being the dose-limiting toxicity. Anemia and thrombocytopenia were also seen. Unfortunately, except for one preliminary report in ovarian cancer,[21] results from several non-randomized phase II trials evaluating the 21-day infusion in a variety of tumor types do not support a substantial improvement in efficacy over the standard daily for 5 days regimen.[20] Of a small group of 16 previously-treated
patients with ovarian cancer, 37% responded, but the confidence limits were wide (95% CI, 12% to 62%).[21] Furthermore, how many of these previously treated patients were truly platinum refractory is unknown. Additional data to complete the assessment of this method of topotecan administration is forthcoming.

A possible explanation for the lack of substantial improvement with prolonged infusion schedules comes from in vitro laboratory experiments. Intermittent repeated topotecan exposures are six times more potent than prolonged continuous exposures, and the continuous exposures result in a decreased number of drug-stabilized DNA-topo isomerase I cleavable complexes in medulloblastoma cells.[115] This decrease is associated with translocation of the topoisomerase I enzyme from the nucleus to the cytoplasm. Because the amount of cleavable complex formed may correlate with topotecan efficacy, continuous-exposure schedules may be less effective than prolonged intermittent administration. This theory has not been tested clinically.

Topotecan Combination Regimens

Topotecan’s single agent activity in ovarian cancer and small-cell lung cancer has provided the rationale for the development of regimens that combine topotecan with other agents active in these diseases. Clinical trials have recently established the recommended phase II solid tumor doses of topotecan in combination with cisplatin,[116,117] paclitaxel,[118,119] cyclophosphamide,[120] doxorubicin,[121] and etoposide.[122-124] The combination of topotecan and cytarabine has also been studied in acute leukemia.[97] Most of these regimens combine a DNA-damaging agent with topotecan, which can potentially interfere with DNA repair.[125] However, caution must be used when combining the camptothecin topoisomerase I inhibitors with other agents with overlapping toxicities.

In many cases, substantial dose reductions of both drugs are required when topotecan is combined with other myelosuppressive agents (Table 3). Pharmacokinetic interactions may also complicate the development of topotecan combination regimens. For example, the sequential administration of cisplatin followed by topotecan was found to generate significantly more myelosuppression than the alternate sequence.[117] This increased toxicity was attributed to the decreased clearance of topotecan resulting from the subclinical renal tubular toxicity that may have been induced by cisplatin.[117]

Recently, a three-arm randomized phase II study that included two different topotecan combination regimens demonstrated severe myelosuppressive toxicity and an unanticipated number of toxic deaths after treatment with topotecan and cisplatin or topotecan and paclitaxel.[126] Fatal treatment-related sepsis occurred in 3 of 12 patients receiving topotecan and cisplatin and in 3 of 12 patients receiving topotecan and paclitaxel, leading to a temporary suspension of the trial. In retrospect, the definition of dose-limiting toxicity as neutrophil counts ≤ 500/mm³ for more than 7 days or febrile neutropenia in the phase I trials that preceded this study[116,118] was too aggressive for application to a larger phase II population of extensive-stage, small-cell lung cancer patients. This experience highlights issues that must be carefully considered when developing drug combinations with topoisomerase I-targeting agents.

Conclusions

Topotecan is an active drug for the treatment of human cancer with efficacy demonstrated in ovarian cancer, small-cell lung cancer, non-Hodgkin’s lymphoma, myelodysplastic syndromes, and pediatric neuroblastoma and rhabdomyosarcoma. In the United States, topotecan has been approved for use in previously treated patients with advanced ovarian cancer. Preliminary data suggesting that the drug may also have activity in acute leukemia has provided the impetus for additional clinical evaluation. Further trials to better define its spectrum of activity, particularly in combination with other anticancer drugs, are ongoing.

The myelosuppressive toxicity of the currently approved topotecan regimen is high, and it is unclear whether this degree of toxicity is essential for optimal antitumor activity. When used with other agents, reduced doses of drugs are required because of myelosuppressive toxicities. To date, phase II trials of 21-day continuous infusions of topotecan do not suggest substantially greater efficacy than that obtained in trials using the standard 5-day regimen. A promising and important area for clinical study is the evaluation of topotecan combinations as initial therapy for patients with ovarian cancer and small-cell lung cancer. Although these diseases are often initially responsive to chemotherapy, they remain difficult to cure. Completion of ongoing phase III studies incorporating topotecan into front-line combination chemotherapy should demonstrate whether topotecan can...
meaningfully prolong survival and increase cure rates in these diseases. As a new agent with a novel
mechanism of action, topotecan is an additional tool with the potential to improve current therapy
for human cancer.

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