Clinical Status and Optimal Use of Topotecan

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The development of topotecan (Hycamtin) and the encouraging preliminary results of its use in clinical trials are comprehensively reviewed by Takimoto and Arbuck. The successful development of topotecan demonstrates that focused research and developmental efforts by the pharmaceutical industry in anticancer therapeutics can actually “pay off.” Approximately 15 years ago, the prototypic topoisomerase I inhibitor camptothecin was “placed back on the shelf” because it induced severe, unpredictable toxicity when administered as a sodium salt (sodium camptothecin). After recognition that camptothecin was active by virtue of a novel mechanism of action (topoisomerase I inhibition), developmental research efforts at SmithKline Beecham led to the synthesis of a myriad of camptothecin analogs, significant structure-function information, and the ultimate selection of topotecan as a lead camptothecin analog for clinical development.[1-3]

In addition to considerations regarding potency and preclinical efficacy, the principal criteria used by SmithKline Beecham investigators in selecting topotecan included its intrinsic topoisomerase I-targeting activity (in contrast to activity as a prodrug) and its aqueous solubility. Those properties eliminated the need to formulate the agent in an atypical vehicle and to administer high doses of it as an inactive salt—which was probably the reason for many of the noxious toxicities associated with sodium camptothecin.

Other Camptothecin Analogs

Similar efforts by other pharmaceutical companies, such as Yakult Honscha, resulted in the discovery and clinical development of irinotecan (CPT-11 [Camptosar]), which received regulatory approval in the United States for use in patients with drug refractory or recurrent advanced colorectal cancer. In other countries, it was approved for use in patients with advanced colorectal and lung cancers.[4]

There are also many water-soluble camptothecin analogs now in clinical development. Furthermore, due to recent advances in pharmaceutical chemistry and the availability of many novel formulations and drug delivery vehicles, the administration of even more potent, water-insoluble camptothecin derivatives, which might portend vastly different spectra of antitumor activity, toxicity, and clinical applicability, is undoubtedly feasible at this time. It is also likely that our current appreciation of the potential clinical ramifications of topoisomerase I inhibition, based on preliminary results of clinical evaluations of topotecan and irinotecan to date, merely represent the “tip of the iceberg” with regard to this class of anticancer compounds.

Differences in Spectra of Activity

One of the most important questions pertaining to the camptothecin analogs concerns the reasons for the substantial differences in their spectra of antitumor activity and adverse effects. At this time, it is not clear whether such differences may be attributed to physicochemical characteristics (eg, water solubility, kinetics of lactone ring opening, and/or potency of topoisomerase I inhibition), pharmacologic characteristics (eg, clearance, metabolism, tissue distribution), and/or unique mechanisms of intrinsic and acquired resistance (eg, p-glycoprotein overexpression conferred by multidrug resistance [MDR]).

The magnitude of topotecan resistance conferred by MDR in vitro is much lower than that noted with
classic MDR substrates, such as doxorubicin or vinblastine. In fact, the low level of this resistance led many investigators to evaluate whether protracted 21-day IV infusions every 4 weeks and/or high doses of topotecan, 3.5 mg/m²/d for 5 days plus granulocyte colony-stimulating factor (G-CSF [Neupogen]) every 3 weeks, might, in fact, overcome drug resistance in patients with colorectal cancer and other neoplasms derived from tissues constitutively overexpressing MDR. For the most part, both attempts to overcome topotecan resistance potentially due to MDR have been largely unsuccessful to date at least in patients with colorectal cancer. [References 5 and 6; and E. K. Rowinsky, MD, et al, unpublished data, 1997] However, little is known about the relevance of MDR in conferring either inherent or acquired clinical resistance to topotecan in colorectal cancer and other malignancies in the first place.

**Dosing Schedule Strategies**

It is likely that our current expectations regarding the optimal use and potential utility of topotecan may also represent the tip of the iceberg. Like so many other antineoplastic agents now in use, clinical empiricism guided the selection of topotecan’s currently approved dosing-schedule[1.5 mg/m² as a 30-minute IV infusion daily for 5 days every 3 weeks. In essence, this intermittent dosing schedule represents a hybrid or compromise between protracted administration that simulates optimal pharmacologic conditions required for maximal cytotoxicity (ie, prolonged or continuous drug exposure) and more pragmatic schedules that favor convenience and overall clinical feasibility. The currently approved schedule is tolerable, and even more importantly, has notable objective activity against a wide range of tumors, including recurrent and refractory ovarian cancer, small-cell lung cancer, refractory leukemia, non-Hodgkin’s lymphoma, and pediatric solid tumors (the latter is reviewed by Takimoto and Arbuck). In addition, there have been some attempts to rigorously evaluate the relationship between topotecan dose and response and to determine whether the maintenance of a critical dose or dose intensity is important.

At this juncture, there is even a paucity of data to guide clinicians in their decision to reduce doses of topotecan or add hematopoietic colony-stimulating factor support as an initial or subsequent maneuver in those who experience intolerable neutropenia. However, it is likely that both ongoing and future evaluations designed to optimize topotecan dosing, scheduling, and its incorporation into combination regimens will enhance topotecan’s therapeutic index and overall applicability.

**Oral Formulation**

The prospects for simulating the optimal pharmacologic conditions required for maximal in vitro cytotoxicity will ultimately be enhanced by the availability of a feasible oral topotecan formulation, obviating the need for ambulatory IV infusion pumps to administer topotecan for prolonged periods.[7,8] In addition, the use of an oral formulation will likely minimize the achievement of high peak plasma concentrations, which may be a critical pharmacologic determinant for several adverse effects, while maximizing the duration at which biologically effective or critical plasma concentrations are exceeded. The feasibility and pharmacologic characteristics of oral formulations have been evaluated in preliminary clinical evaluations, and the oral formulation is currently being evaluated in both phase II and III studies.[7,8]

In one ongoing phase III trial, women with platinum-refractory or recurrent advanced ovarian carcinoma are being randomized to treatment with either topotecan (1.5 mg/m²/day IV for 5 days every 3 weeks) or topotecan (2.3 mg/m²/d orally for 5 days every 3 weeks). Not only is this study assessing conventional end points, such as objective response rates, progression-free survival, and overall survival, but also the study will yield important information enabling valid comparisons regarding convenience, quality of life, toxicity, and the overall therapeutic indices associated with both dosing schedules.

The development of an oral formulation may have several other ramifications affecting topotecan’s clinical utility. For example, a fairly large proportion of patients with many types of malignancies seemed to achieve “stable disease” as their best response and experienced relatively long periods of clinical benefit or stability when treated with topotecan in phase II and III studies. Yet, none ever met the criteria that defined an objective (partial or complete) response. In addition, many of these patients terminated therapy before disease progression actually occurs—a practice that may reflect the personal philosophy of the oncologist and community patterns.

However, the question of whether or not a patient actually achieves a partial or complete response should be considered only when formally screening or evaluating new agents or therapeutic regimens in clinical trials. These criteria should not be the principal index of clinical benefit in everyday practice. By increasing the convenience and possibly the therapeutic index of topotecan, oral formulations may more readily permit the oncologist to continue therapy for prolonged periods.
in situations where an objective antitumor response may not be evident, but there is no obvious evidence of disease progression or symptomatic deterioration.

On a similar note, topotecan’s potential utility in clinical situations in which the agent had formerly demonstrated only [marginal] activity may be much greater than is currently appreciated. In such instances, patients may not have been treated until obvious disease progression, and the true progression-free interval and clinical benefit may not have been fully appreciated. Thus, it is possible that topotecan may have a disproportionately greater impact on progression-free survival (which might be demonstrated more readily in randomized trials) than on reducing the size of tumors by at least 50%. The availability of an oral formulation that is both convenient and feasible may serve as the impetus to reevaluate the utility of topotecan in clinical situations in which the potential benefit of the agent was previously presumed to be negligible based on somewhat inappropriate criteria. These reevaluations should measure the potential of topotecan produce symptomatic benefit, sustain or improve functionality or quality of life, and prolong both progression-free and overall survival.

**Stem-Cell Disorders**

In addition to the notable clinical activity of topotecan in ovarian cancer, small-cell lung cancer, and non-Hodgkin’s lymphoma, preliminary results of phase II studies in patients with myelodysplastic syndromes are intriguing.[9] Although both conventional cytotoxic and noncytotoxic agents can induce objective responses in this group of relatively unrelenting stem-cell disorders, the fact that a high proportion of patients with karyotypic abnormalities become cytogenically normal after treatment with topotecan is particularly noteworthy. The high rate of severe toxicity in these patients who received topotecan at its maximally tolerated leukemia dose (2 mg/m²/d as a continuous 5-day IV infusion) is not surprising as this population often consists of elderly individuals with a high incidence of concurrent serious medical illnesses.

At this juncture, it would seem prudent to pursue two developmental directions for topotecan in myelo- dysplastic syndrome. On the one hand, the exploration of more aggressive [induction regimens,](perhaps combinations of topotecan and cytarabine and/or other relevant agents), might be warranted to determine whether topotecan-based regimens can increase complete clinical and cytogenetic response rates, as well as response durability. On the other hand, less intensive regimens, perhaps consisting of low doses of topotecan as a single agent, might have considerable utility as a less toxic, convenient outpatient therapy that can be administered chronically, either continuously or intermittently. The oral formulation might prove to be considerably useful for this purpose.

**Drug Combination Therapy**

There are few anticancer agents in our therapeutic armamentarium that have had a significant therapeutic impact when used alone, particularly in treating patients with solid neoplasms. Similarly, it is not likely that the full therapeutic potential of topotecan will be realized until it is optimally combined with other chemotherapy agents and/or radiation. As discussed by Takimoto and Arbuck, the cytotoxic effects of the combination of topoisomerase I-targeting agents and alkylating or platinating agents are exquisitely sequence-dependent.[10] For the combination of topotecan and cisplatin (Platinol), the most profound cytotoxic effects (antitumor effects in preclinical studies and toxicity in phase I studies) have been noted when treatment with cisplatin precedes topotecan. While these sequence-dependent effects in vitro may be attributed to the inherent synergy between the platinating/alkylating agents and topoisomerise I-targeting agents (perhaps due to the inhibitory effects of camptothecin analogs on the repair of DNA damage or un-scheduled DNA synthesis induced by platinum or alkylating agents), the profound cytotoxic and toxicologic differences noted in both preclinical and clinical investigations may be due, in part, to sequence-dependent pharmacologic interactions. With the sequence of cisplatin (day 1) followed by topotecan (days 1 to 5), topotecan’s pharmacological exposure progressively increases from day 1 to 5, due possibly to a degree of subclinical renal toxicity induced by cisplatin. Diminished topotecan clearance rates and greater drug exposure are the end results compared to the reverse sequence. Regardless of the precise etiology of these sequence-dependent interactions, the maximum tolerated doses of both cisplatin and topotecan in the [optimal] sequence of cisplatin followed by topotecan are substantially lower than the doses that many clinicians consider to be [clinically relevant]. However, the combination of topotecan and cisplatin should not be [written off] as unfeasible because of an inability to administer applicable single agent doses of both agents. Instead, the inability to administer [clinically relevant] single-agent doses of both agents in combination might result from [synergistic hematologic toxicity], which reflects the fact that true therapeutic synergism may be occurring in neoplastic tissues as well. Based on topotecan’s significant activity in
patients with recurrent or refractory small-cell-lung and ovarian cancers, the combination of cisplatin and topotecan should be considered an ideal candidate for evaluation in previously untreated patients.

**Topotecan and Radiation**

A similar argument can be made to support the rationale for pursuing developmental evaluations of topotecan and radiation, which have also demonstrated synergistic cytotoxic activity in preclinical studies most likely on the same basis as that discussed previously for combinations of topotecan and alkylating/platinating agents.[10] In view of the preliminary results of phase II studies of topotecan to date, combined- modality treatment of patients with radiation and topotecan might be particularly useful as primary therapy for those with glioma, stage II or III non-small-cell lung cancer, and limited-stage small-cell-lung cancer. Likewise, further clinical evaluations of the combination of topotecan and topoisomerase II-targeting agents (eg, etoposide [Vepesid], and doxorubicin) are warranted because of the therapeutic synergism observed in preclinical evaluations, (although antagonistic interactions with simultaneous treatment have also been noted).[10] Several rational therapeutic developmental targets for such combination regimens, based on preliminary results of phase II studies to date, might include small-cell-lung cancer, lymphoma, leukemia, and pediatric solid tumors such as neuroblastoma and rhabdomyosarcoma.

The unique distributive characteristics of topotecan across the blood-brain barrier into the central nervous system are a pharmacologic attribute that may be specifically applied to the treatment of neoplasms with a high propensity to involve the central nervous system and other sanctuary sites. The potential utility of topotecan in these settings is perhaps best illustrated by the preliminary results of a phase II study of topotecan (1.5 mg/m$^2$/d for 5 days every 3 weeks or 0.4 mg/m$^2$/day as a continuous IV infusion for 21 days every 4 weeks) in patients with small-cell lung cancer and brain metastases following the failure of first-line therapy.[11] Of 16 evaluable patients, some of whom had previously received brain irradiation, 4 complete responses and 6 partial responses occurred, and the objective response rate of central nervous system metastases was 63%.

**Summary**

Topotecan should not be written off as a boutique drug with only limited applicability in selected malignancies. This presumption may reflect our current limitations and excessive rigidity in designing and interpreting the results of early clinical studies of new anticancer agents. Instead, the results of both preclinical and clinical studies to date indicate that topotecan's potential clinical utility may be far from realized. The agent's favorable toxicity profile and the projected high feasibility and applicability of an oral formulation support this view. It is also clear that our current body of knowledge with regard to optimal dosing, scheduling, and use with other chemotherapy agents is deficient, and clinical evaluations focusing on optimizing the use of topotecan are greatly needed.

**References:**


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