Topoisomerase I Inhibitors

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ABSTRACT

Topoisomerase I inhibitors are a new class of anticancer agents with a mechanism of action aimed at interrupting DNA replication in cancer cells, the result of which is cell death. Most if not all Topoisomerase I inhibitors are derivatives of the plant extract camptothecin. Irinotecan (CPT-11), a semi-synthetic derivative of camptothecin, is approved in the United States for the treatment of colorectal cancer. Ongoing clinical trials with CPT-11 show a 13% to 32% response rate when it is used singly or in combination with other chemotherapeutic agents such as 5-fluorouracil. The major dose-limiting toxicities of CPT-11 are myelosuppression and a dual phase diarrhea. Topotecan is another semi-synthetic analogue of camptothecin. It is approved for use in the United States for the treatment of cisplatin refractory ovarian carcinoma. Current clinical trials suggest antitumor activity against a variety of human tumor types. There is significant interindividual variability in the plasma disposition of this drug. The main dose-limiting toxicity is myelosuppression. There are other derivatives of camptothecin, as well as new formulations of the parent plant extract, that are in various stages of clinical trials. Some of these clinical trials are aimed at increasing the therapeutic benefits of the agents when used singly or in combination with other chemotherapeutic agent(s) or treatment modalities. The dose-limiting toxicity observed in most of these clinical trials is myelosuppression.

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INTRODUCTION

Clinical trials with compounds targeting eukaryotic DNA topoisomerases for cancer control have shown promising results. Topoisomerases (Topo) are DNA enzymes that control the topology of the supercoiled DNA double helix during the transcription of replication of cellular genetic materials. There are two major types of topoisomerases, Topo I and II [1]. Topo I initiates the cleavage of a strand of DNA molecule while Topo II cleaves both DNA strands. These actions guarantee the subsequent replicative process of the DNA. The partial or complete inhibition of this DNA replicative mechanism results in the accumulation and stability of cleavable complexes and subsequent death of the cell [1, 2]. Though this is widely accepted as the main mechanism by which Topo I inhibitors produce their antitumor effect, the mechanism by which this class of drugs achieves selective toxicity in cancer cells is not fully understood. Another proposed model for the antitumor effect of Topo I inhibitors suggest that the accumulation or prolongation of Topo I cleavable complexes results in irreversible DNA replication defects and subsequent cell cycle arrest and cell death [3]. Consequently, tumors that express significantly high levels of Topo I enzyme are presumed to be easy targets for Topo I inhibitors. The cytotoxic effect of Topo I inhibition depends on the length of exposure and not so much on the concentration of the Topo I inhibitor [3]. Thus the schedule of administration is likely to be an important determinant of tumor response. There are currently several Topo I inhibitors being studied in ongoing clinical trials. Of these, only two, namely topotecan and irinotecan (CPT-11), have been approved. Both drugs are semisynthetic derivatives of a plant alkaloid, camptothecin (CPT) [4, 5]. The other Topo I inhibitors in clinical trials include CPT, NB-506, GI147211 and 9-aminicamptothecin (9-AC) [6-12].

CPT-11

This is a water-soluble semisynthetic analog of CPT. It is metabolized mainly by the liver to 7-ethyl-10-hydroxycamptothecin (SN-38). This metabolite is pharmacologically active and accounts for a significant portion of the antitumor activity of irinotecan [13]. Iyer et al. have shown that SN-38...
is glucuronidated by a specific isozyme of hepatic uridine diphosphate glucuronyltransferase (UGT1A1) to the corresponding glucuronide (SN-38G) [14]. This same hepatic enzyme is also responsible for bilirubin glucuronidation. A gene defect has been described in promoter sequence upstream of UGT1A1 exon I as well as in the coding sequence [15], thus suggesting the possibility of genetic polymorphism in the metabolism of SN-38.

Antitumor Activities

In preclinical studies, CPT-11 demonstrated significant antitumor activity in a broad spectrum of experimental human tumor xenografts and murine tumor models. This CPT analog has been shown to have substantial antitumor activity against human tumor xenografts derived from adult and pediatric central nervous system malignancies [16]. Vassal et al. observed that CPT-11 showed strong antitumor activity against peripheral primitive neuroectodermal tumor and chemotherapy-naive neuroblastoma xenografts that had markers suggestive of poor prognosis [17]. Also, preclinical studies showed CPT-11 to have significant antitumor effects against spontaneous lung metastases in colon C26 and Lewis lung carcinoma [18]. CPT-11 demonstrated activity against human tumor cell lines resistant to vincristine, doxorubicin, colchicine, and vinblastine [19].

Clinical Trials

CPT-11 is approved for use in the United States for refractory metastatic colorectal cancer. It has a significant antitumor activity in 5-fluorouracil (5-FU)-resistant colorectal cancer [20]. Phase II studies of patients with colorectal cancer demonstrated response rates of between 13% and 32% in both chemotherapy-naive patients and patients pretreated with 5-FU [20-23]. Masuda et al. noted a 47% partial response rate when CPT-11 was used to treat refractory or relapsed small cell lung cancer in 15 patients with prior chemotherapy exposure [24]. Using a weekly dose of 100 mg/m² of CPT-11 single agent therapy, Fukuoka et al. observed a 32% response rate in chemotherapy-naive patients with non-small cell lung cancer [25]. In other clinical trials, CPT-11 has also been found to possess promising antitumor activity in patients with squamous cell carcinoma of the uterine cervix or skin, soft tissue sarcomas, and mesotheliomas [26]. Other cancers that have been known in clinical trials to respond impressively to CPT-11 include those of the pancreas, breast, ovary, cervix, and non-Hodgkin’s lymphoma [26, 27]. CPT-11 demonstrates promising synergistic antineoplastic activity when combined with platinum-based compounds, 5-FU alone, 5-FU/leucovorin, 5-FU/folinic acid, or docetaxel alone [28-32].

Pharmacokinetics

Model-dependent analysis of mean population pharmacokinetic parameters showed CPT-11 to have either a biphasic or triphasic terminal half-life of 12 h, with a total-body clearance of 14.8 l/m²/h. The terminal half-life is the same when the pharmacokinetic parameters are derived using a model-independent analysis [33]. In the adult population, age does not influence the pharmacokinetics of CPT-11 or its metabolites [34]. There is paucity of data regarding the use of CPT-11 in pediatric oncology. Vassal et al. reported on an ongoing phase I study in children with refractory or recurrent solid tumors. So far, no dose-limiting toxicity has been observed at a 300 mg/m² dose every three weeks [35]. The total-body clearance of CPT-11 in the pediatric population was about the same as in adults (16 ± 5.8 l/m²/h versus 12.8 l/m²/h). While there might be a drug-drug interaction between CPT-11 and the platinum-based compound oxaliplatin [29], no such interaction was reported with other drug combinations. Ongoing phase I studies using prolonged infusion schedules suggest substantial inter- and intra-individual variability in drug exposure [36]. CPT-11 is metabolized mainly in the liver to an active metabolite, SN-38. It has also been shown that CPT-11 is converted to SN-38 by carboxylesterase present in non-small cell lung cancer cells [37]. SN-38 undergoes enterohepatic circulation. Chabot et al. evaluated 107 patients in a phase I trial and found that while about 17% of administered CPT-11 is excreted in the urine in a 24-h period, the amount of SN-38 recovered in the urine represented 0.23% of the CPT-11 does. They found that physiological characteristics of a patient do not seem to affect total-body clearance or the metabolic ratio of CPT-11 and its metabolite; however, total-body clearance of the drug is lower in women than in men. Also, there is a significant correlation (negative) between CPT-11 total-body clearance and bilirubinemia and gamma-glutamyl transpeptidase [38].

Resistance Profile

Irinotecan does not demonstrate any susceptibility to the P-glycoprotein mediated multidrug resistant phenotype [19]. In vitro resistance to CPT-11 has been shown to be due to mutations and reduced expression to the DNA Topo I gene. However, this mechanism does not fully explain clinically acquired resistance [39]. Matsumoto et al. have speculated that observed resistance by glioma cell lines to CPT-11 was partially due to glutathione-dependent enzyme [40].

Toxicity Profile

Definition of the maximum tolerated dose (MTD) for CPT-11 is still the subject of various clinical studies that are ongoing. The MTD is subject to dosing schedule. The widely accepted treatment regimen is 90 min i.v. infusions of 125 mg/m² weekly times four with a
two-week rest period between cycles. Phase I/II studies done in Europe, Japan, and the United States to define the MTD for CPT-11 include: a 30 mg/m² infusion for five days, a 90-min infusion of 240 mg or 250 mg/m² once every three or four weeks, a 90-min infusion of 100 mg/m² to 150 mg/m² weekly and a 30-min infusion of 350 mg/m² every three weeks [22, 27]. The dose-limiting toxicity (DLT) with high doses of CPT-11 in clinical trials was a grade 3 or 4 neutropenia and a dual phase grade 4 diarrhea. The early (early-onset) phase diarrhea occurs within 30 min of CPT-11 infusion, while the late (late-onset) or delayed diarrhea occurs usually in about one week [2, 27, 41]. The early-onset diarrhea is thought to be cholinergic in origin; thus, anticholinergic therapy is beneficial. However, the mechanism for the delayed-onset diarrhea is not fully elucidated, but is thought to be secretory in nature. It is suggested, but not proven, that the severity of the late-onset diarrhea correlates with the concentration of the active metabolite SN-38 [42].

Current studies are ongoing in our institution to further characterize the mechanism underlying the delayed-onset diarrhea. Preliminary results suggest that the inhibition of the biliary excretion of SN-38 with the use of cyclosporine (5 mg/kg) decreases the severity of the late-onset diarrhea [43]. Conceivably, increasing the metabolism of SN-38 to its corresponding glucuronide SN-38G should also alleviate the late-onset diarrhea, thus allowing for an improved therapeutic index. The caveat in this approach is that patients with suboptimal/deficient UGT1A1 activity may be at increased risk for CPT-11 toxicity [14]. Also high-dose loperamide (2 mg or 4 mg every two h) has been used to modulate the late onset diarrhea in phase II studies in Europe [27, 41]. At a dose of 250 mg/m², prominent cholinergic symptoms were reported within 80 min (range 17 min to 23.4 h) of infusion; in severe cases, atropine was used to treat the symptoms [44]. Other toxicities that have been observed in clinical trials but that are of no clinical significance included asthenia, alopecia, nausea, vomiting and a reversible hepatotoxicity.

**TOPOTECAN**

Topotecan is a water-soluble semisynthetic analog of CPT. Reduced albumin binding in vivo has been shown to be responsible for promoting its stability and activity in humans [45]. It was the first of the CPT derivatives to undergo clinical trials in the United States.

**Antitumor Activities**

Preclinical and clinical studies have demonstrated topotecan to have significant antitumor activity against a variety of human cancer cell lines [46] and human solid tumors (including small-cell lung, breast, esophageal, head and neck primaries, colon ovarian, osteosarcoma, and rhabdomyosarcoma), myelodysplastic syndrome, chronic myelomonocytic leukemia, and B-lineage acute lymphoblastic leukemia in SCID mouse models [47-51]. However, results from phase II clinical trials did not show encouraging antitumor activity of topotecan against other common adult tumor types such as renal cell cancer, prostate cancer, colorectal cancer, chronic lymphocytic leukemia, and non-small cell cancer [52-54]. Combined with cyclophosphamide for treatment of refractory leukemia, preliminary data suggest activity [55].

**Clinical Trials**

Topotecan is approved for use in the United States for cisplatin-refractory ovarian carcinoma. Ongoing phase II and III clinical trials have shown topotecan to be effective against advanced ovarian cancers that were refractory or resistant to prior platinum-based chemotherapy regimens [56]. Preliminary phase I and II clinical trials of topotecan in pediatric and adult central nervous system malignancies are promising [57]. Pediatric phase I trials with topotecan in children with relapsed solid tumors show significant antitumor activities [58]. Topotecan has been shown to potentiate radiation lethality in a concentration and time-dependent manner; the lethality is irreversible [47, 57]. When combined sequentially with a Topo II inhibitor for synergy, in vitro studies suggest that the administration of the Topo II inhibitor should be preceded by topotecan [59]. Suffice it to say that there are ongoing clinical studies investigating the use of topotecan in combination with other chemotherapeutic agents.

**Pharmacokinetics**

Phase I studies of the drug in several dosing schedules ranging from 30 min to three weeks demonstrated a plasma decay profile fitting a two-compartment model with a half-life of two to three h. Elimination of the drug is by the renal route, which accounts for about 30% to 40% of the excreted dose; thus, renal dysfunction may decrease topotecan plasma clearance [60, 61]. There is significant interindividual variability in the handling of topotecan, although the pharmacodynamic variability is relatively small [61, 62]. In the pediatric population, pharmacokinetically guided topotecan dose adjustments have been used to attain a reduction in interpatient variability in topotecan exposure [61]. The oral bioavailability of topotecan is 30% ± 7.7%; thus, the use of this drug orally on a chronic basis could potentially result in significant systemic exposure [63]. There is a reported drug-drug interaction with phenytoin which results in an increased clearance of topotecan [64].
Toxicity Profile

The side effects of topotecan are mostly hematological. Granulocytopenia is the dose-limiting side effect of this drug. Other rare side effects associated with the use of topotecan included nausea, vomiting, elevated liver enzymes, peripheral neuropathy, headache, dermatitis, conjunctivitis, renal, and psychiatric symptoms.

Emerging Topo I Inhibitors

There are other Topo I inhibitors that are in various stages of drug developments. CPT was the first identified Topo I inhibitor; however, clinical studies using a water-soluble sodium salt form of the drug proved to have very severe toxicities (myelosuppression and hemorrhagic cystitis) in the initial clinical trials. Subsequently, analogs of the drug that were less toxic and more water soluble were developed. These analogs comprise the other Topo I inhibitors being reviewed in this article. Notwithstanding, ongoing clinical trials of new formulations of CPT do suggest that the antitumor effects of CPT can be enhanced by sequential combination with a Topo II inhibitor, etoposide [6]. Clinical trials using the oral formulation of CPT show that there is variability in intestinal absorption which is not pH-dependent and that the administration of this drug with acidic juices may not be beneficial [12].

9-aminocamptothecin (9-AC) is a water-insoluble synthetic analog of CPT. In preclinical studies, it demonstrated active antitumor properties against human tumor xenografts. Ongoing phase I studies suggest this drug has improved therapeutic index with prolonged administration [8, 10]. Mani et al. in a phase I study observed the colloidal dispersion formulation of 9-AC to have a very poor bioavailability and saturable absorption [9].

NB-506 is a compound that inhibits Topo I, RNA polymerase II, and DNA polymerase alfa [7]. Phase I studies suggest myelosuppression as the dose-limiting toxicity.

Last, Emerson et al. have reported on two water-soluble CPT analogs (GI147211 and GI149893), with promising antitumor activities in human colon xenograft models [11, 65]. In a phase I trial with GI147211 using 30 min infusion daily for five consecutive days every three weeks, the dose limiting toxicity (neutropenia and thrombocytopenia) was reached at a dose of 1.5 mg/m² [11].

Conclusion

Topo I inhibitors area a relatively new class of antitumor agents which certainly possess strong antitumor activity against a variety of tumor types. In the treatment of colorectal cancer, ovarian cancer, and non-small cell lung cancer, the use of Topo I inhibitors, either alone or in combination with other chemotherapeutic agent(s) or modalities of therapy, have shown encouraging outcomes. Ongoing and future clinical studies with the various drugs in this class of compounds will further define the chemotherapeutic usefulness as well as dose-related toxicities of the Topo I inhibitors.

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