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Clinical Pharmacokinetics and Toxicity of Irinotecan

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Abstract

Topoisomerases are nuclear enzymes involved into the processes of DNA replication and transcription. Irinotecan a semi-synthetic analogue of Camptothecin, is a pro-drug converted at the liver and at the intestinal level by the enzyme carboxylesterase into the active metabolite SN-38, with an enhanced antitumor activity. The SN-38, like other topoisomerase I inhibitors, causes an irreversible double-strand rupture that leads to cell death.

The main pharmacodynamics characteristics of Irinotecan are described, focusing on its adverse effects and clinical use.

Actually, Irinotecan is widely used, alone or in combination with other chemotherapeutics, for the treatment of different tumors, including mainly carcinomas (colon, stomach, lung, ovary and uterus), lymphomas, and pediatric tumors such as neuroblastoma, rhabdomyosarcoma, PNET and brain tumors. Irinotecan metabolism is a complex process, involving numerous effective proteins both in the activation to SN-38 and in the reactions leading to biliary or renal elimination of the drug and its metabolites. The main toxicity is gastrointestinal, mainly nausea and vomiting and delayed diarrhea, and more rarely mucositis and neutropenia. The adverse effects occur with a significant interindividual variability for both onset and severity.

Promising possibilities to customize and optimize therapy with Irinotecan to reducing adverse reactions while increasing clinical efficacy, based on the predictive role of gene markers have been recently reported.

Keywords: Irinotecan, toxicity, pharmakinetics, SN-38, topoisomerase, diarrhea

Introduction

In 1966 an alkaloid present in a tree of Chinese origin, the Campthotheca Acuminata, called Camptothecin (CPT), was identified as an agent with a significant anticancer action in murine models of leukemia through interaction with topoisomerases type I(1).

Topoisomerases are nuclear enzymes involved in the processes of DNA replication and transcription. Their activity influences the degree of overturning of the double helix, by cutting and subsequent tracing of the phosphodiesteric DNA skeleton, so allowing the maintenance of the three-dimensional structure of the DNA.

The DNA replication process requires a transient "relaxation and unwinding" of the double DNA helix to allow the advancement of the "replication fork". To reduce the torsional

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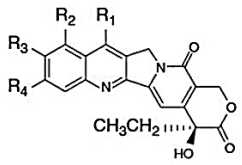
tensions of the double helix, transient cuts in the DNA chain are required. Topoisomerase I allows relaxation of the torsional tensions to which the DNA is subjected in the replication and transcription phases causing breakages in a single DNA chain to allow rotation around the intact chain (cleavable complex) and then repair of the ruptures to reconstitute the double DNA helix. CPT interacts with the Topoisomerase I-DNA complex by stabilizing the so-called "cleavable complex" between Topoisomerase I and DNA, causing the initially reversible breaks to become irreversible hindering the activity of the proteins flowing along the DNA (heliasis, DNA polymerase) and preventing the strengthening of DNA until the initiation of apoptosis, thus leading to cell death (2).

Erroneously defined inhibitors, the anticancer drugs of this class should be classified as topoisomerasae interactive agents, since the activity of the enzyme is partially related to their cytotoxic effect.

Despite a significant antitumor activity observed in the first clinical studies in the 1960s, the use of CPT was limited by severe and unpredictable toxicities (mainly myelotoxicity and hemorrhagic cystitis). Therefore, efforts were finalised to the synthesis of CPT analogues with the aim of overcoming the two main factors limiting the development of these drugs: myelotoxicity and poor water solubility.

Thus, water-soluble semi-synthetic analogues of CPT were identified. They are characterized by pentacyclic structures with a lactonic ring, whose integrity is an essential requirement for optimal interaction with Topoisomerase I: the lactonic ring is in equilibrium in aqueous solution with the relatively inactive open hydroxyacid form. Currently, three semi-synthetic analogues are available in clinical practice: Irinotecan, Topotecan and 9-aminocamptotecine (Figure 1).



Compound	Molecular weight	R_1	R_2	R_3	R_4
Camptothecin	348.36	–H	–H	–H	–H
Topotecan	421.46	–H	$-CH_2N(CH_3)_2$	–H	–H
Irinotecan	586.69	$-CH_2CH_3$	–H	-O-C(=O)-N⟨⟩-N⟨⟩	–H
SN-38	392.42	$-CH_2CH_3$	–H	–OH	–H

Figure 1. Structure of CPT and semi-synthetic analogues.

Irinotecan

Irinotecan (7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxycamptothecin) is a pro-drug and, following intravenous infusion, is converted by the enzyme carboxylesterase into the active metabolite SN-38, with 100 to 1000 times higher antitumor activity (3).

This activation takes place mainly at the liver level, but also at the intestinal level. In addition, some cancer cells can convert Irinotecan into its active metabolite (4).

Its active metabolite (SN-38), like other topoisomerase I inhibitors, usually causes non-lethal DNA damages to cancer cells. However, damages are not repaired so causing an irreversible double-strand rupture due to the collision between the advancing and operating DNA polymerase at the replicating fork level and the SN-38-stabilized complex. Therefore, the rupture inhibits the binding of the DNA, blocks the synthesis of nucleic acid, and leads to a cascade of events that culminate with cell death (5).

Pharmacokinetics

The plasma peak plasma of Irinotecan occurs immediately after the infusion has been completed while for its active metabolite SN38 is later, occurring 30 to 90 minutes after the end of the infusion. The half-life time (t1/2)

of Irinotecan (9 to 14 hours), as well as that of the lactonic form of SN38 (over 13 hours), is very high especially when compared to other similar drugs, such as Topotecan. The elimination of Irinotecan occurs mainly through biliary excretion, while urinary excretion of the compound appears to be only 10-22% of the dose administered.

The pharmacokinetics of Irinotecan is linear and increases proportionally with the administered dose, following a linear pharmacokinetics and this implies that the dose administered, and the diet do not affect total plasma clearance or the large volume of distribution. For SN-38 it has not yet been clarified whether its kinetics is linear or whether at high doses a plateau can be reached due to saturation of the pathways of Irinotecan metabolism. Irinotecan metabolism is a complex process, involving numerous effective proteins both in the activation of the drug in SN-38 and in the reactions leading to biliary or renal elimination of the drug and its metabolites (6).

After intravenous infusion, the Irinotecan in the plasma is balanced between the lactonic (active) and carboxylated (inactive) forms, while the lactonic form is predominant at physiological pH. In this conformation, the promedication can penetrate the plasmatic membranes essentially by passive diffusion and once inside the cell. Then, it is converted into its active metabolite SN-38 by hydrolysis catalyzed by isoforms 1 and 2 of the human carboxylesterase (hCES1, hCES2), microsomal enzymes present in the serum, intestine, tumor tissue and, at high concentrations, in the liver (7).

This metabolic process, at the level of the human liver, is particularly slow, probably because of the low affinity for this family of enzymes. In general, hCES show a higher catalytic activity to the lactonic form of Irinotecan and this can partly explain the predominance of the active lactonic form and of the plasmatic SN-38 of patients receiving the promedication (8).

This property, combined with the low activation rate exhibited by this enzyme, has a significant influence on the clinical activity of Irinotecan, as it contributes to achieve in vivo a slow release of the active metabolite, optimal condition for achieving the best cytotoxic effect. In fact, the potentially lethal complexes of CPT with topoisomerase I and DNA become reversible in the minutes following the removal of the drug, so the constant plasma concentration indicates stability of the complex for longer time (9,10).

In addition to the activation process, Irinotecan can also undergo oxidative metabolism by P-450 cytochrome 3A4 and 3A5 isoforms (CYP3A4 and CYP3A5), expressed at high levels in the human liver and transforming it into several non-pharmacologically active derivatives, mainly 7-ethyl-10-[4-N-(5 aminopentanoic acid)-1-piperidine] carbonyloxy-camptothecin (APC) and 7-ethyl-10-(4-amino-1-piperidine) carbonyloxy-camptothecin (NPC) (11).

Both APC and NPC have no pharmacologically relevant cytotoxicity. However, NPC may play a functionally important role, as it appears to be a substrate for hCES and thus lead to the formation of additional SN38(12). Finally, the detoxification of Irinotecan involves the transformation of SN-38 into its inactive derivative by conjugation reaction with a glucuronic acid molecule, catalyzed by enzymes belonging to the uridine-glucoronosyltransferase 1A family (UGT1A) and mainly UGT1A1, UGT1A7 and UGT1A9 isoforms (13-16).

This metabolic step not only inactivates the drug but is useful for the transformation of SN-38 into a more water-soluble metabolite (SN-38G) and therefore more easily excreted through the urine and bile. SN-38 is then metabolized at the liver level by the enzyme uridine-diphospho-glucoronosyltransferase (UGT) in the form SN-38G, and then eliminated by bile. This enzyme is the same implicated for the bilirubin metabolism, so patients with high

levels of bilirubin or with UGT deficiency (Gilbert or Crigler-Nijar syndrome) or receiving drugs that inhibit UGT, may be at risk of increased toxicity as well as toxicity is often associated with the UGT1A1*28/*28 genotype.

SN-38G is the predominant form of SN-38 in vivo at both plasma and urinary level, while it is poorly present into the stool, although the biliary tract is recognized as an important removal route.

This is related to the bacterial β-glucuronidases present in the intestinal lumen that can hydrolyse the inactive form SN-38G and thus regenerate the active metabolite SN-38. The latter, due to the enteroepathic recirculation, is made available again and is responsible for the late toxic effects of irinotecan such as tissue damage and diarrhea (17).

Several studies have shown significant drug interactions between Irinotecan and other therapeutic agents that modulate positively or negatively the activity of proteins involved in the Irinotecan metabolic processes with important clinical implications. Particular attention should be reserved to the administration of Irinotecan together with inductors or inhibitors of P-450 cytochrome, UGT system and proteins involved in the transport of Irinotecan and its metabolites for the risk of severe toxicity.

Clinical activity

Irinotecan is a drug widely used, alone or in regimens of association with other chemotherapeutic, for the treatment of different cancers, including mainly some carcinomas (colon, stomach, lung, ovary, uterus), lymphomas and recurrent pediatric tumors (18-22).

In preclinical studies, Irinotecan showed high antitumor activity in vitro and in vivo against a broad spectrum of murine and human tumor cell lines. Numerous clinical trials in adults have confirmed this anticancer activity of Irinotecan towards different tumors (colon, breast, prostate, stomach, lung, brain, ovary, lymphoma and leukemia).Irinotecan is currently approved in several countries for the treatment of colorectal cancer as a second-line drug in patients resistant to 5-Fluoro-Uracil therapy and as a first-line drug in combination with 5-Fluoro-Uracil and folinic acid.

In particular, initially in 1996 the FDA approved the use of Irinotecan for the treatment of patients with colorectal cancer who relapsed or were undergoing progression after therapy with 5-fluorouracil (5-FU). Later, in 2000, the Irinotecan, in association with 5-FU (FOLFIRI) and leucovorin (LV), was approved as a first-line therapy of metastatic colorectal cancer and is now one of the standard options for the treatment of this cancer (23).

The same combination of chemotherapy (CPT-11+5-FU+LV) represents, in a context where there is a poor chance of second-line therapy, an important emerging treatment option for metastatic pancreatic adenocarcinoma in patients who have progressed after gemcitabine therapy. A recent review that reports the positive experience of this triplet chemotherapy in patients with metastatic pancreas cancer, however, highlights the use for the first time of Irinotecan hydrochloride trihydrate in a liposomal pegylated formulation (nal-IRI or MM-398 or PEP02)(24,25).

The encapsulation of the drug in a macromolecular carrier such as a liposome is an excellent strategy aimed at improving the therapeutic index; preclinical studies have documented better pharmacokinetics and a more advantageous safety profile of this formulation than that of free Irinotecan. Promising data have also been obtained from the use of this chemotherapy for the treatment of other neoplasms such as lung cancer both small and small cells (NSCLC and SCLC), breast, ovarian and cervical cancer and various gastrointestinal and cerebral cancers)(26,27).

Although less studied than in adults, Irinotecan seems to be a promising new

drug in the treatment of pediatric tumors. An important antitumor activity has been observed in xenografts derived from pediatric tumors such as neuroblastoma, rhabdomyosarcoma, PNET and brain tumors (28-30). The use of Irinotecan in phase I and II studies initially revealed a lower response rate than in preclinical studies. This difference is largely explained by the schedule-dependence of this chemotherapy due to its high specificity for the S phase of the cell cycle that requires prolonged exposure to adequate concentrations to obtain maximum cytotoxic activity.

Different schedule of administration were used: a single infusion every 3 weeks; a weekly infusion for 4 weeks; a daily infusion for 5 days every 3 weeks; a daily infusion for 5 days a week for two weeks every 3 weeks.

In the study of Vassal et al. Irinotecan was administered as a single dose every 3 weeks to 81 pediatric patients with different solid refractory tumors or relapses after conventional treatment. Irinotecan was administered at doses between 200 and 720 mg/m^2. The maximum tolerated dose (MTD) was 600 mg/m^2; dose-limiting toxicity (DLT) at such doses was myelooxycity in heavily pre-treated patients (cranial-spinal irradiation or high-dose chemotherapy) and diarrhea in conventionally treated patients. In this study, 4 partial responses and 21 disease stability were obtained from 81 patients (31).

In the study of Bomgaars et al. Irinotecan was administered in a weekly dose for four consecutive weeks every 6 weeks. Twenty-three pediatric patients received doses between 125 and 200 mg/m^2/dose. MTD was 125 mg/m² for heavily pre-treated patients and 160 mg/m² for naive patients; DLT was myelotoxicity and diarrhoea in heavily pre-treated patients, only myelotoxicity in not heavily pretreated patients. About its anticancer activity, there were 5 disease stability out of 23 patients (32).

Blaney et al. performed a phase I study in which Irinotecan was administered at a dose of 30 to 65 mg/m^2/day daily for 5 days every 3 weeks. MTD was 39 mg/m^2 for heavily pre-treated patients and 50 mg/m^2/day for patients who had received non-intensive treatment. DLT was neutropenia, which affected less than 20% of heavily pre-treated patients, and diarrhea that affected 2/3 of patients. Among the 30 patients evaluated, 2 partial responses and 7 stable disease were recorded (33).

In the Phase I study of Furman et al., 23 patients with solid tumours refractory to conventional treatment were treated with Irinotecan infusion at a dose between 20 and 29 mg/m^2/day for five days a week for two weeks every 3 weeks. DLT was diarrhea. MTD for this schedule was identified as 20 mg/m^2/day. Out of 23 patients examined, 5 had a partial response and 16 stable disease (34).

According to the results of preclinical studies, Irinotecan appears to possess a cytotoxic activity mainly linked to the schedule of administration with a higher rate of responses in case of prolonged administration. In fact, the schedule is based on the administration of low daily doses for a prolonged period (5 days x 2 weeks with 2 days interval every 3 weeks) seems to record an increase in anticancer activity compared to schedule using the same dosage but with a shorter administration time.

Toxicity

The main toxicity observed with the Irinotecan is represented by the gastrointestinal toxicity (acute cholinergic syndrome or late onset diarrhea) and by the myelotoxicity (especially neutropenia). The toxicity is mainly linked to the schedule of administration used. Diarrhea is the dose-limiting toxicity with continuous or intermittent administration, while in case of single administration, it is the myelotoxicity to represent the main DLT.

Neutropenia is the main haematological toxicity and is reversible and not cumulative. A severe neutropenia (grade III-IV) is present in

26 to 46% of patients; it is usually short-lived and neutropenia febrile occurs only in a minority of cases (3-6%)(35).

Other adverse reactions related to myelosuppression induced by the drug are leukopenia, anemia and more rarely thrombocytopenia. This important myelosuppression linked to Irinotecan seems to be related to the cytotoxic effect of the active metabolite SN-38 on bone marrow cells.

Late diarrhea, on the other hand, represents the most frequent (40-60% of treated cases) and the most important non-haematological toxicity: it can be severe (grade III-IV) in 37% of cases.

It usually occurs at 5 - 12 days from the administration and has a duration of 2-5 days, although the most severe episodes can have a longer duration, up to 7 days. It is a secretive-exudative diarrhea, related to the cellular apoptosis of the ileal epithelium and to the mucous hyperproduction at the level of the caecum: if prolonged in time and not promptly treated, it can lead to dehydration, malnutrition, electrolytic imbalance, and sepsis (36-40).

The severity of diarrhea can be reduced by the use of loperamide. In order to reduce this negative effect, it is generally carried out a prophylaxis with cefixima, a bactericide belonging to the class of third-generation cephalosporins that inhibits the synthesis of the cell wall of the bacterium, or neomycin, which acts by reducing the production of β-glucuronidase by bacterial flora. In fact, it is assumed that this severe form of late diarrhea is associated with an increase in the concentration of the active metabolite SN-38 at the level of the intestinal mucosa. This local increase in turn may be due: 1) to the conversion into SN-38 of Irinotecan and the metabolite NPC, excreted through the hepatobiliary tract, by means of intestinal hCES. 2) to the conversion into the active form of SN-38G, derived from the bile or activity of the intestinal enzyme UGT1A7, by endogenous bacterial β-glucuronidases. 3) to the direct hepatobiliary excretion of SN-38 (40,41).

Since bacteria with β-glucuronidase activity can be eliminated from antibiotics, it has been shown that the use of these drugs can lead to a reduction in the acute effect of late diarrhea and damage to the caecum (42).

Studies have also shown that antibiotic therapy, while at the intestinal level induces a decrease in the concentrations of the active metabolite SN-38 and a concomitant increase in the glucuronate form, at the plasma level does not lead to any change in the levels of Irinotecan, SN38 or SN38-G (43).

Further side-effects, due to damage caused by the active metabolite at the level of the intestinal mucosa, are nausea and vomiting (12-20%). These symptoms appear during or immediately after the starting of administration of the drug while asthenia and alopecia are rare (44-50). All adverse manifestations are registered with a significant inter-individual variability both for the possible onset and for the degree of severity. Inter-subjective variability was, in some cases, associated with different plasma levels of the active metabolite SN-38 and appeared to be the result of inter-complex relationships between multiple metabolic pathways whose activity is influenced by different factors including the genetic differences of the proteins involved (51-54).

However, the individual differences and the low number of cases included do not allow assessing any potential adverse vascular events in patients with malignant glioma treated with bevacizumab plus Irinotecan (55).

Promising possibilities to customize and optimize therapy with Irinotecan, reducing adverse reactions to the drug and increasing the clinical efficacy have been recently reported based on the use of predictive gene markers (56-58).

Conclusion

Irinotecan is a crucial antineoplastic drug for the treatment of several solid cancers. Many factors can contribut to the large interindividual pharmacokinetic variability although much progress has been made in unraveling the pharmacogenetic influence on systemic exposure, toxicity, and survival. Future research should prospectively address the benefit of individualized Irinotecan treatment based on patient characteristics, and pharmacogenetics. Furthermore, novel drug formulations, such as liposomal forms of Irinotecan, could help to pharmacologically optimize its treatment.

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Conflict of interest statement

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Authors' contributions

All authors participated in the research design, data analysis, and the writing of the manuscript. All authors approved the final version of the manuscript.

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