Journal of Exploratory Research in Pharmacology **2026** vol. 11(2) | e00002
DOI: 10.14218/JERP.2026.00002

Review Article

Irinotecan-induced Neutropenia: A Comprehensive Review of Pathogenesis, Risk Factors, and Management

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Received: January 28, 2026 | **Revised:** March 25, 2026 | **Accepted:** April 28, 2026 | **Published online:** May 21, 2026

Abstract

Irinotecan is a camptothecin derivative that exerts its antitumor effects by metabolizing into the active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38). It is widely used clinically for treating various advanced solid tumors. However, irinotecan frequently induces neutropenia, predisposing patients to infection and even death. This review aims to provide a theoretical basis for the clinical management of irinotecan-induced neutropenia (IIN). Irinotecan and SN-38 mainly induce hematopoietic stem cell damage and dysfunction by inhibiting topoisomerase I and triggering mitochondrial injury, which ultimately results in neutropenia. Notably, the risk factors of IIN include irinotecan dosage, gene polymorphism, individual baseline characteristics, and drug combination. And several strategies effectively prevent IIN, such as adjustment of drug dosage, genotype testing, oral alkalinizing drugs, supplement of granulocyte colony-stimulating factor, and regulation of intestinal microorganisms. In summary, this review systematically elaborates on the classification, epidemiology, pathogenesis, risk factors, and management strategies of IIN, with the goal of providing references for the clinical prevention and management of irinotecan-related adverse reactions.

Introduction

Irinotecan is a semisynthetic, water-soluble derivative of camptothecin. It is enzymatically converted by carboxylesterase into the active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38), which exhibits cytotoxicity 100 to 1,000 times greater than that of irinotecan. Both irinotecan and SN-38 function as topoisomerase I inhibitors, specifically targeting the S phase of the cell cycle. They inhibit DNA synthesis, thereby suppressing malignant tumor cell proliferation and inducing apoptosis.[1,2] Irinotecan is widely used in the treatment of metastatic or advanced solid tumors, particularly gastrointestinal cancers.[3,4] However, its clinical use is associated with multiple adverse effects, including gastrointestinal reactions, bone marrow suppression, and liver dysfunction. Among these, neutropenia (NP) is one of the most common and severe adverse reactions linked to irinotecan therapy. Dosage is a critical clinical determinant of both the risk and severity of this adverse effect, and the toxicity demonstrates dose-dependent as well as dose-limiting characteristics.[5,6]

Neutrophils serve as the primary cellular component of innate immune defense (beyond epithelial barrier protection) against invading pathogens and account for 50–70% of circulating leukocytes. These cells are characterized by numerous cytoplasmic antimicrobial granules. Upon pathogenic challenge, neutrophils rapidly mobilize and infiltrate sites of inflammation, where they exert key antimicrobial effector functions.[7,8] NP is a hematological disorder typically defined as an absolute neutrophil count (ANC) of less than 1.5×10^9/L in peripheral blood.[9,10] NP not only necessitates reduced chemotherapy doses and delayed or interrupted therapy, thereby diminishing therapeutic efficacy, but also heightens infection risk and mortality rates.[11] This review systematically summarizes the classification, epidemiology, pathogenesis, risk factors, and management strategies of IIN, aiming to provide a reference for the clinical prevention and standardized management of irinotecan-associated adverse reactions.

Keywords: Irinotecan; SN-38; Neutropenia; Pathogenesis; Risk factors; Management strategies.

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How to cite this article: Zhang L, Tian C, Li W, Lan Y, Shu C, Zhang C. Irinotecan-induced Neutropenia: A Comprehensive Review of Pathogenesis, Risk Factors, and Management. *J Explor Res Pharmacol* 2026;11(2):e00002. DOI: https://doi.org/10.14218/JERP.2026.00002.

Classification and epidemiology of IIN

Although no definitive classification criteria for NP currently exist, NP can be categorized into acute and chronic forms based on its duration. Acute NP lasts no longer than three months and is typically induced by cytotoxic agents or infections. Chronic NP persists for more than three months and is usually congenital (e.g., cyclic NP, variants of Kostmann syndrome) or associated with autoimmune disorders.[12] IIN falls under the category of acute NP, which increases the risk of infection and leads to treatment interruption. Consequently, close monitoring of hematological parameters is required during irinotecan administration, with timely dose adjustments based on clinical response.

According to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 6.0, the grading of NP is specifically defined as follows: Grade 1: ANC of (1.5 to <2.0) × 10^9/L; Grade 2: ANC of (1.0 to <1.5) × 10^9/L; Grade 3: ANC of (0.5 to <1.0) × 10^9/L; Grade 4: ANC < 0.5 × 10^9/L.[13] Grades 3 and 4 are considered severe NP, the severity of which is influenced by the chemotherapy regimen and specific genetic profiles. Patients with Grade 3–4 NP face an increased risk of infection and sepsis, and those with Grade 4 NP are particularly prone to hospitalization due to fever.[14]

Patients treated with irinotecan exhibit a high incidence of bone marrow suppression, primarily manifested as NP, with the peak incidence typically occurring on day 8 after administration.[15] A recent study further confirmed that irinotecan-induced neutropenia is a common hematologic toxicity associated with irinotecan treatment.[16] Furthermore, a Phase III RESILIENT trial indicated that among 229 patients treated with irinotecan, 8.0% experienced Grade 3–4 NP.[17] In a comparative Phase III clinical trial evaluating two irinotecan dosing regimens—weekly (once a week for four weeks followed by a two-week rest period) versus once every three weeks—for metastatic colorectal cancer, up to 34% of patients receiving irinotecan chemotherapy developed Grade 3–4 NP.[18] Additionally, another study demonstrated that the incidence of severe NP was 33.3% in patients receiving a high dose of irinotecan (125 mg/m²), whereas it was only 16.7% in those receiving a slightly lower dose (100 mg/m²).[19] In summary, the reported incidence of IIN varies considerably across studies, which can be attributed to the combined effects of multiple factors, including sample size, dosage, treatment cycle, and individual differences among study populations.

Pathogenesis of IIN

Irinotecan enters the bloodstream and is primarily metabolized in the liver, where carboxylesterase converts it into the active metabolite SN-38, which drives its antitumor effects and toxicity (especially NP).[20] In the liver, uridine diphosphate-glucuronosyltransferase (UGT) 1A1 converts SN-38 into inactive SN-38 glucuronide (SN-38G), which is excreted into the intestine via bile. In the gut, β-glucuronidase from intestinal bacteria reconverts a portion of SN-38G back to SN-38, which is reabsorbed (Fig. 1). Unchanged irinotecan may also undergo direct biliary excretion.[21] Due to interindividual enzyme variability, plasma SN-38 concentrations vary considerably and correlate closely with NP. Clinical studies have found that plasma SN-38 concentrations are closely associated with NP. In colorectal cancer patients treated with the FOLFIRI regimen, elevated plasma SN-38 concentrations are significantly positively correlated with the severity of NP, and a reduced SN-38G/SN-38 ratio in patients can further exacerbate NP.[22] In addition, another study found that the FOLFIRI regimen results in higher SN-38 exposure than the IRIS (irinotecan/S-1) regimen, with a significantly higher incidence of NP (100.0% vs. 33.3%).[23] Therefore, irinotecan primarily induces NP through SN-38.

Irinotecan induces NP by inhibiting TOPO I in hematopoietic stem cells (HSCs)

Irinotecan is a potent inhibitor of TOPO I. However, its inhibitory activity against this enzyme is only 1/100 to 1/1,000 that of SN-38. Both irinotecan and SN-38 form stable complexes with the TOPO I–DNA interface, inducing single-strand breaks that subsequently lead to double-strand breaks upon replication fork collapse. This triggers a robust DNA damage response, thereby blocking DNA replication.[16] While exerting antitumor effects, both agents also cause significant cytotoxicity to proliferating normal cells, particularly HSCs in the bone marrow, leading to bone marrow suppression.[24,25] HSCs are self-renewing, multipotent stem cells residing in the bone marrow that give rise to various blood cell lineages, including granulocyte progenitor cells, which further differentiate into mature neutrophils.[26] The number and functional integrity of HSCs critically influence the efficiency of neutrophil production.[27] Owing to the short half-life of neutrophils (6–8 h), SN-38 impedes neutrophil production and reduces peripheral blood neutrophil counts by suppressing the function and proliferative capacity of HSCs, ultimately inducing NP.[28] Given the high sensitivity of HSCs and their progenitor cells to DNA damage, these agents likely induce NP primarily through damage to HSCs and their downstream precursor cells (Fig. 2).

Irinotecan induces NP by damaging mitochondria in HSCs

Irinotecan can induce mitochondrial damage through multiple mechanisms. Its active metabolite, SN-38, is lipophilic and readily crosses the mitochondrial membrane, where it inhibits electron transport in the mitochondrial respiratory chain and promotes the generation of reactive oxygen species (ROS). In addition, irinotecan inhibits mitochondrial-specific topoisomerases, thereby disrupting the normal structure and replication of mitochondrial DNA (mtDNA). This leads to mtDNA damage and subsequent mitochondrial dysfunction. Damaged mtDNA downregulates the expression of mitochondrially encoded genes, including MT-COII, MT-ND1, and MT-CYB, further exacerbating mitochondrial structural abnormalities and functional impairment.[29,30] Mitochondrial dysfunction, in turn, promotes ROS production. Excessive ROS not only perpetuates mitochondrial damage (including mtDNA injury and disruption of mitochondrial architecture), thereby establishing a vicious cycle, but also induces nuclear DNA damage. Given that both mitochondrial dysfunction and DNA damage can trigger apoptosis in HSCs, irinotecan may contribute to NP by inducing mitochondrial injury in HSCs (Fig. 2).[30-32]

Risk factors of IIN

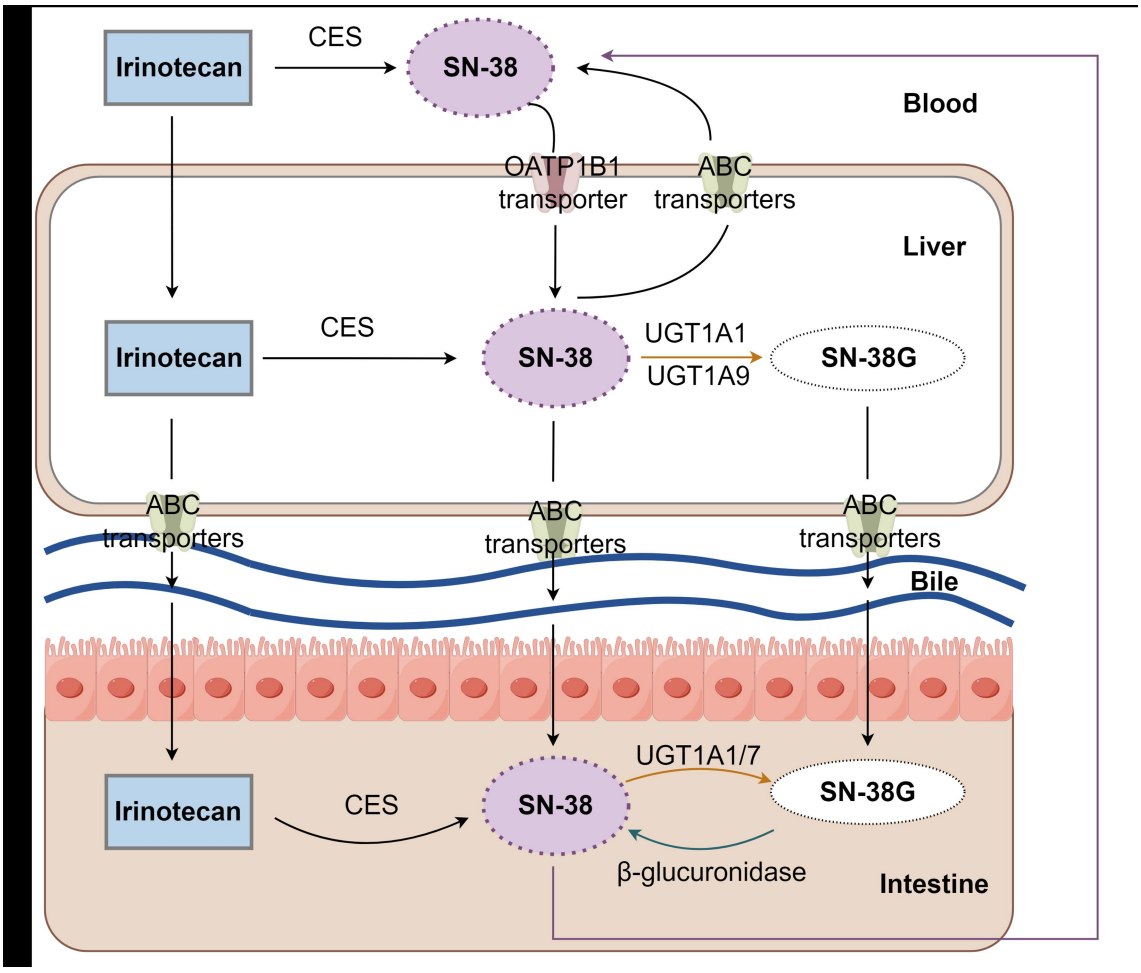

Fig. 1. Metabolism of irinotecan *in vivo*. Irinotecan is metabolized by carboxylesterase (CES) into the active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38). SN-38 can enter the liver via organic anion transporting polypeptide (OATP) 1B1 transporters and be transported out of the liver via ABC transporters. Within the liver, it is catalyzed by uridine diphosphate-glucuronosyltransferase (UGT) 1A1 and UGT1A9 into the inactive metabolite SN-38 glucuronide (SN-38G). Irinotecan and SN-38 are also excreted into the intestine via ABC transporter-mediated biliary secretion. In the intestine, irinotecan is metabolized by CES into SN-38, which is then glucuronidated by UGT1A1 and UGT1A7 to form SN-38G. SN-38G can also be converted back to SN-38 by β-glucuronidase.

Dosage of irinotecan

The dosage of irinotecan is the primary determinant of IIN and exhibits a positive correlation with its occurrence. In a Phase I clinical and pharmacokinetic study of irinotecan for the treatment of advanced solid tumors, results from the first chemotherapy cycle indicated that the incidence of Grade 3–4 leukopenia was 27% in the 100 mg/m² dose group. As the dose was further increased, bone marrow suppression worsened markedly, with the incidence of Grade 3–4 leukopenia reaching 40% in the 115 mg/m² dose group. Additional clinical data have corroborated this dose–response relationship.[33] Compared with the 60 mg/m² dose group, the incidence of NP in the 80 mg/m² dose group was significantly higher (0% vs. 66.7%).[34] Another study demonstrated that among patients treated with 125 mg/m² irinotecan, the incidence of severe NP was 33.3%, whereas it decreased to only 16.7% when the dosage was reduced to 100 mg/m².[19] Furthermore, the initial dose of irinotecan is also closely associated with the risk of NP. It has been confirmed that among patients receiving a high initial dose (150 mg/m²) of irinotecan, the incidence of Grade 4 NP was as high as 67%, significantly higher than that in patients receiving a low initial dose (120 mg/m²), which was 20%.[14] Therefore, reasonable and precise control of irinotecan dosage is of great significance in reducing the risk of NP.

UGT1 gene polymorphism

The UGT1 family is a member of the UGT superfamily and belongs to the phase II drug-metabolizing enzymes.[35] Among this family, UGT1A1, UGT1A7, and UGT1A9 catalyze the glucuronidation of SN-38, thereby playing a critical role in its inactivation and clearance (Fig. 1).[36] Consequently, reduced activity or expression of these enzymes leads to SN-38 accumulation and promotes the development of IIN.

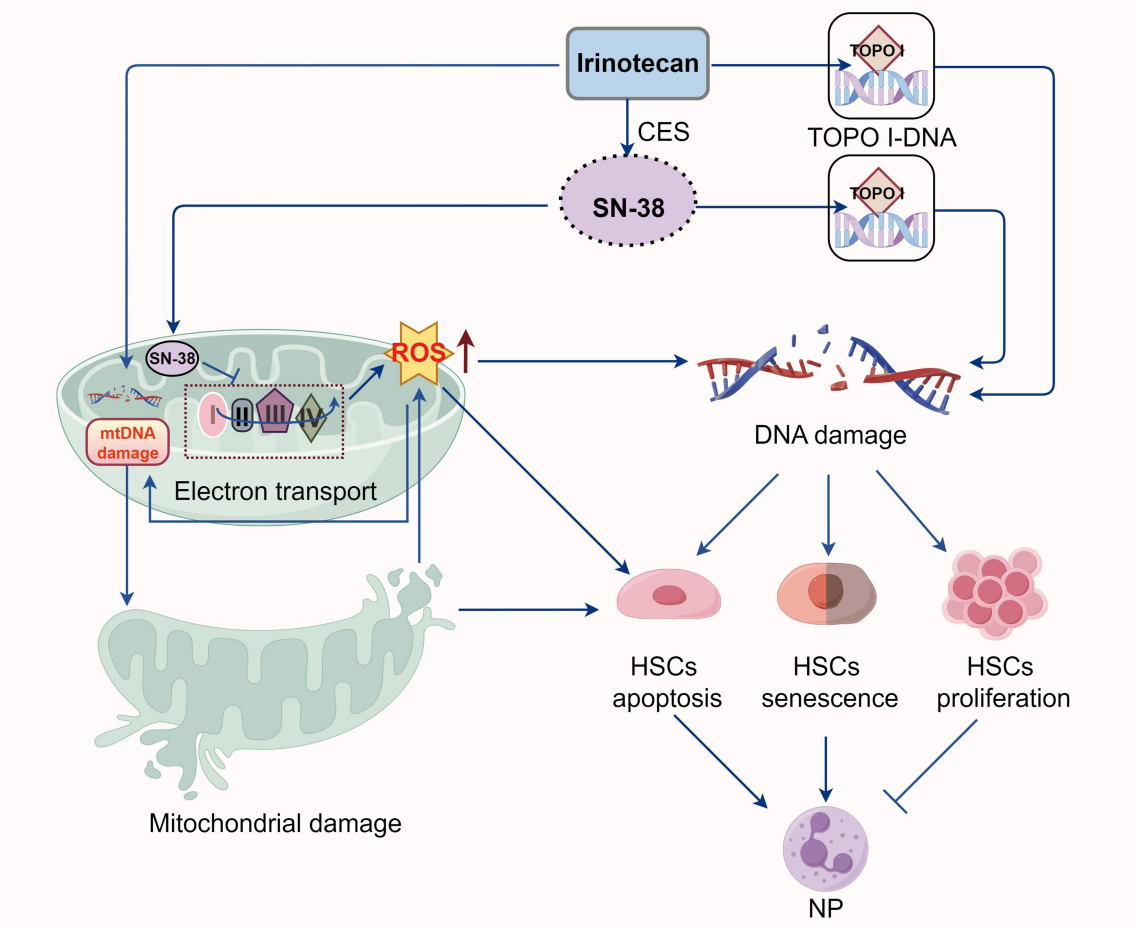

Fig. 2. Pathogenesis of irinotecan-induced neutropenia (NP). Both irinotecan and 7-ethyl-10-hydroxycamptothecin (SN-38) inhibit topoisomerase I (TOPO I) and form stable complexes with TOPO I–DNA, resulting in DNA damage. In addition, irinotecan can damage mitochondrial DNA, leading to structural disruption and mitochondrial dysfunction. SN-38 also penetrates the mitochondrial membrane and inhibits electron transport in the mitochondrial respiratory chain, thereby promoting the production of large amounts of reactive oxygen species (ROS). Excessive ROS not only further aggravates mitochondrial injury and forms a vicious cycle but also exacerbates DNA damage and promotes apoptosis of hematopoietic stem cells (HSCs). Mitochondrial dysfunction can directly induce HSC apoptosis, while DNA damage arrests HSC proliferation and accelerates their senescence and apoptosis, ultimately causing NP. CES, carboxylesterase; mtDNA, mitochondrial DNA.

Patients carrying the UGT1A1*6 variant, which decreases UGT1A1 activity, exhibit a 71.4% incidence of Grade 3–4 NP, significantly higher than that in patients without this variant (35.3%, $P = 0.022$).[37] The U.S. Food and Drug Administration has designated UGT1A1*28, a variant that reduces UGT1A1 expression, as a warning marker for irinotecan toxicity risk.[38] In a prospective study (N = 66) of single-agent irinotecan, patients (predominantly White) carrying the UGT1A1*28/*28 genotype had a higher risk of Grade 4 NP compared with those carrying UGT1A1*1/*1 or *1/*28 (relative risk (RR) = 9.3; 95% confidence interval (CI): 2.4–36.4).[39] Furthermore, polymorphisms in UGT1A7 and UGT1A9 are also associated with IIN occurrence. The UGT1A7 subtype is primarily expressed in the gastrointestinal tract, and UGT1A7*3 represents an enzyme-deficient genetic variant.[40] Carriers of the UGT1A7*3 allele exhibit a significantly increased incidence of Grade 3–4 NP ($P < 0.004$) when receiving irinotecan (180 mg/m²).[38] Additionally, UGT1A9*22 has been associated with IIN.[41] Therefore, clinicians should closely monitor patients carrying UGT1A1*6, UGT1A1*28, UGT1A7*3, and UGT1A9*22 for the development of IIN.

Gene polymorphisms of transporters associated with SN-38

In addition to UGT1 family members, transporters involved in SN-38 disposition are also closely associated with IIN. Organic anion transporting polypeptide (OATP) 1B1, encoded by the solute carrier organic anion transporter family member (SLCO) 1B1 gene, is an organic anion transporter specifically distributed on the basolateral membrane of hepatocytes and participates in the hepatic uptake of various endogenous and exogenous substances.[42,43] OATP1B1 also serves as an essential transporter for the entry of SN-38 into hepatocytes (Fig. 1), as SN-38 must be taken up via OATP1B1 to undergo subsequent glucuronidation.[44] Therefore, reduced OATP1B1 expression or decreased transporter

affinity for SN-38 can both lead to diminished glucuronidation of SN-38 within hepatocytes, resulting in SN-38 accumulation. 521T>C is a common single nucleotide polymorphism in the SLCO1B1 gene associated with IIN. This variant results in a valine-to-alanine substitution at amino acid position 174 of the encoded OATP1B1 transporter, reducing its affinity for substrates and consequently impairing its transport activity.[45] East Asian patients carrying this variant have a two- to fourfold increased risk of developing IIN.[46] Accordingly, patients with this mutation should receive targeted preventive measures during irinotecan therapy to reduce the risk of NP.

ABC transporters constitute the largest family of membrane transport proteins. ABC transporters, including ABCC1, ABCC2, ABCB1, and ABCG2, regulate the efflux of SN-38 from the liver into bile. Consequently, increased SN-38 exposure correlates with genetic polymorphisms in these ABC transporters.[47] Increased expression of ABCC1, also known as multidrug resistance-associated protein (MRP) 1, may elevate systemic SN-38 levels, thereby reducing the ANC. ABCC2 (also designated MRP2) is expressed in the liver, kidneys, and small intestine and serves as a key transporter for the biliary excretion of irinotecan and SN-38. Its expression levels are closely linked to the clearance rates of irinotecan and its metabolites (Fig. 1).[48] The ABCC2 c.3972C>T polymorphism has been positively associated with the occurrence of NP ($P < 0.012$), and patients carrying this polymorphism are more prone to developing severe NP during the first cycle of chemotherapy.[49]

Individual baseline characteristics

In addition to the aforementioned factors, age (particularly ≥ 65 years), gender, hepatic and renal function, and tumor type are also risk factors for the occurrence of severe IIN.

Age

Among patients receiving irinotecan therapy, Grade 3 and 4 NP is more prevalent in those over 65 years of age.[50] Consequently, elderly patients are more susceptible to developing severe NP following irinotecan treatment, a phenomenon that may be attributed to altered pharmacokinetics and pharmacodynamics, as well as an increased prevalence of chronic comorbidities.[51] With advancing age, changes in organ function and body composition modify the tissue distribution of irinotecan and SN-38 and prolong the duration of drug exposure.[50] As a result, elderly patients face a heightened risk of toxicity when administered standard doses of irinotecan.

Gender

Numerous biological differences exist between women and men, which may lead to variations in the pharmacokinetic behavior of drugs between female and male patients. For certain medications administered at identical doses, women exhibit not only significantly higher blood concentrations than men but also a longer elimination time.[52] Women exhibit relatively higher exposure to irinotecan, making them more prone to developing NP in clinical settings.[53] This phenomenon can be partially explained by reduced metabolic clearance of SN-38.

Liver and kidney function

In pharmacokinetic studies of irinotecan, patients with elevated serum levels of aspartate aminotransferase, alanine aminotransferase, and total bilirubin exhibited a higher ratio of the area under the plasma concentration–time curve (AUC) of SN-38 to that of irinotecan.[50] Given that the AUC of SN-38 correlates with the incidence and severity of irinotecan toxicity, patients with impaired liver function face a higher risk of adverse effects. The glucuronidation of SN-38 in the liver is primarily catalyzed by UGT enzymes responsible for bilirubin metabolism (i.e., bilirubin-UGT). Furthermore, serum bilirubin level is a significant covariate for irinotecan and SN-38 exposure. One study found that for patients with a serum total bilirubin concentration ≥ 0.8 mg/dL, the irinotecan dose should be reduced to less than 80 mg/m² when using a weekly dosing regimen.[54] Consequently, patients with Gilbert's syndrome or other hereditary glucuronidation defects exhibit an increased risk of IIN.[55]

Additionally, as irinotecan and SN-38 are partially eliminated via the kidneys, impaired renal function may result in reduced excretion of these agents or their metabolites. Patients with lower creatinine clearance (35–66 mL/min) face a fourfold increased risk of Grade 3–4 NP when treated with irinotecan compared with those with normal renal function ($P < 0.001$).[56] This is likely because reduced excretion leads to drug accumulation and increased systemic exposure, ultimately triggering toxic reactions.[57]

Others

The incidence of IIN is also associated with multiple non-genetic factors, including cancer type, individual habits, and low baseline neutrophil counts. Patients with advanced tumor stages (T2–T4 staging) undergoing irinotecan therapy exhibit a higher incidence of severe NP compared to those with T0 to T1 tumor staging.[58] Interestingly, smoking reduces the incidence of severe IIN. The incidence of Grade 3–4 NP following irinotecan treatment is 6% among smokers, compared with 38% among non-smokers. This disparity arises because smokers exhibit more extensive glucuronidation of SN-38, resulting in reduced systemic exposure to the active metabolite SN-38.[59]

Drug combination

Irinotecan is commonly used in combination with other chemotherapeutic agents for the clinical treatment of malignant tumors; however, such combinations may exacerbate the toxicity of irinotecan. Notably, when combined with platinum-based agents (e.g., oxaliplatin or cisplatin), as in the FOLFOXIRI regimen, the additive myelosuppressive effects are more pronounced. For instance, the incidence of NP is significantly higher with irinotecan plus cisplatin than with irinotecan monotherapy. Specifically, the incidence of NP is 24% in patients receiving irinotecan alone, compared with 57.1% in those receiving the combination regimen.[60] Furthermore, relative to irinotecan monotherapy, the combination of irinotecan with 5-fluorouracil is associated with a significantly increased incidence of severe NP (RR = 1.23; 95% CI: 1.01–1.51).[61]

Prevention and management strategies for IIN

Genotype testing

To ensure medication safety, genotype testing is recommended prior to initiating irinotecan therapy.[62] Adjusting the dosage and

treatment regimen of irinotecan based on the patient's genotype is a critical measure for preventing NP. For example, patients who are homozygous or compound heterozygous for the UGT1A1*28 allele exhibit reduced UGT1A1 enzyme activity when treated with irinotecan, leading to SN-38 accumulation and an increased risk of NP.[63] A model-based clinical simulation study demonstrated that in patients with the UGT1A1*28/*28 genotype, the implementation of UGT1A1 genotyping followed by a 25% reduction in the irinotecan dose would decrease the incidence of severe NP from 45% to 18%.[39] Therefore, a reduced initial dose of irinotecan is recommended for patients carrying the UGT1A1*28 allele. A prospective study on UGT1A1 genotype-guided irinotecan dosing in poor metabolizer patients further showed that this approach enhances safety, maintains therapeutic drug exposure levels, and offers favorable cost-effectiveness.[64] In clinical practice, adjusting irinotecan dosing according to the distribution of genetic polymorphisms across patients of different ethnic backgrounds holds promise for reducing drug toxicity and improving therapeutic outcomes.

Adjustment of drug dosage

In combination therapy regimens, adjusting the irinotecan dosage can reduce the risk of IIN. A study involving patients with advanced colorectal cancer demonstrated that when the irinotecan dose was reduced from 300 mg/m² to 250 mg/m² in a regimen combining intravenous bolus 5-fluorouracil and leucovorin with intravenous irinotecan, the incidence of Grade 3–4 NP decreased significantly from 83% to 63%.[65] Therefore, during combination therapy, careful dose management based on the patient's treatment response and dynamic adjustment of the dosing regimen are essential to enhance medication safety.

Oral alkalinizing drugs

The enterohepatic circulation of SN-38 leads to its delayed excretion, thereby increasing the risk of IIN. Oral alkalinizing agents, such as sodium bicarbonate, magnesium oxide, and ursodeoxycholic acid, can elevate intestinal pH and promote the ionized form of SN-38 within the gut lumen. The ionized form inhibits the enterohepatic circulation of SN-38 and facilitates its elimination from the body, thus reducing the incidence of IIN.[66] Furthermore, supplementation with alkalinizing agents during irinotecan therapy may permit higher and safer dosing levels, enabling the use of more appropriate therapeutic doses and improving both treatment efficacy and safety.

Supplement of granulocyte colony-stimulating factor (G-CSF)

G-CSF has been identified as a key driver of HSC mobilization, potently promoting granulocyte production and release from the bone marrow. This makes it highly effective for the prevention and treatment of NP in cancer patients receiving irinotecan therapy.[67] For high-risk patients, such as those over 65 years of age, females, or those with hepatic or renal impairment, the use of G-CSF is recommended as a primary preventive measure.[68] Furthermore, the timing of G-CSF administration should be tailored to the specific chemotherapy regimen. In each treatment cycle, patients should undergo risk assessment for severe NP to enable timely prophylactic G-CSF administration when indicated. Nevertheless, the high cost of G-CSF preparations may limit patient access to this therapy to some extent.

Regulation of intestinal microorganisms

Intestinal bacterial β-glucuronidase hydrolyzes glucuronidated metabolites in the gut into the toxic moiety SN-38, thereby promoting enterohepatic circulation and exacerbating toxic reactions.[69] Consequently, intervention can be achieved by inhibiting β-glucuronidase. Three older drugs, aspartame, N-desmethylclozapine, and gatifloxacin, have been proven to effectively inhibit β-glucuronidase activity with good selectivity, suggesting their potential as agents for intervening in IIN.[70] Additionally, certain probiotics may represent a potential therapeutic strategy for ameliorating IIN by maintaining intestinal microecological balance and inhibiting intestinal β-glucuronidase activity.[71] Meanwhile, dietary modification offers another potential approach for alleviating IIN. Natural components found in various herbs and fruits, such as flavonoids and cinnamic acid derivatives, also possess β-glucuronidase inhibitory activity, thereby providing alternative intervention strategies for IIN.[4]

Discussion

Irinotecan, as a key chemotherapeutic agent, is widely used in the treatment of malignant tumors.[72] However, its severe and high incidence of NP has limited its clinical application to some extent. IIN is classified as acute NP, with an incidence rate typically reaching 30%.[16] However, the pathogenesis of IIN has not been fully elucidated. Current evidence suggests that irinotecan primarily inhibits TOPO I through its active metabolite SN-38, leading to damage and functional impairment of HSCs. In addition, irinotecan can induce mitochondrial damage via multiple pathways, further exacerbating HSC dysfunction and ultimately contributing to the development of NP. Numerous factors influence the development of IIN, encompassing both genetic and non-genetic components. Among genetic factors, polymorphisms in the UGT1A, SLCO1B1, and ABC transporter genes affect the metabolism and transport of irinotecan and SN-38, thereby promoting NP occurrence. Non-genetic factors, such as patient age, sex, and cancer type, also exert significant influence and should not be overlooked. In particular, drug dosage is the primary clinical determinant of NP.

For the prevention of IIN, strategies based on genotype-guided initial dose setting, combined with dynamic monitoring and dose adjustment during chemotherapy, have effectively reduced its incidence. Current treatments, such as G-CSF, accelerate bone marrow recovery by stimulating HSC proliferation and differentiation, providing rapid relief from NP symptoms. However, these methods are associated with adverse effects, including allergic reactions, headaches, and bone pain.[73] In recent years, antibody–drug conjugates have emerged as a new trend in the clinical application of irinotecan. These agents use target-specific antibodies as carriers to deliver potent cytotoxic agents precisely to tumor cells, thereby exerting antitumor effects while reducing damage to normal cells and consequently lowering toxicity.[74] Meanwhile, intervention strategies based on gut microbiota have also received considerable attention.

However, there are several limitations in this review. First, most clinical trials enroll a small number of patients, resulting in substantial variability in the incidence of IIN. Second, the underlying mechanism of IIN remains poorly elucidated; only a

limited number of studies have explored its pathogenesis, with most investigations merely focusing on HSCs. Third, although existing prevention and treatment strategies for IIN have been summarized, most of them are supported by limited clinical evidence, and there are currently no therapeutic approaches with remarkable clinical efficacy for IIN.

Future directions

Therefore, future research on IIN can be focused on the following directions. First, large-scale clinical trials should be performed to clarify the incidence and major risk factors of IIN. Second, animal experiments are warranted to explore the pathogenesis of IIN and elucidate its underlying molecular mechanisms, so as to develop potential therapeutic strategies. Third, integrated with pharmacogenomics and individualized medication strategies, it is necessary to explore the effects of polymorphisms of key genes such as UGT1A1 on the susceptibility to IIN, establish risk prediction models, and guide precise clinical medication as well as early preventive intervention.

Conclusions

This review comprehensively summarizes the pathogenesis, risk factors, and management strategies of IIN. As a common acute hematological adverse reaction, IIN severely limits the clinical application of irinotecan. Its pathogenesis is primarily associated with the active metabolite SN-38, which inhibits topoisomerase I and induces mitochondrial dysfunction, thereby causing hematopoietic stem cell damage. Genetic and non-genetic factors jointly affect patient susceptibility to IIN, among which drug dosage serves as a vital clinical risk factor. Genotype-based dose optimization can effectively prevent IIN. G-CSF facilitates bone marrow recovery but exhibits unavoidable side effects. In addition, antibody–drug conjugates and gut microbiota interventions represent novel and promising strategies to reduce chemotherapy-related toxicity. By elaborating on the above contents, this review intends to provide a theoretical basis for the clinical treatment of IIN.

Acknowledgments

The authors express their sincere gratitude to Figdraw for the granted image materials.

Funding

This article was jointly supported by the Hubei Provincial Natural Science Foundation and the Huangshi Innovation Development Joint Fund of China (2026AFC0010).

Conflict of interest

The authors have no conflict of interest related to this publication.

Author contributions

Conceptualization and revision (ZCL, SCR), literature review, paper writing, diagramming (ZLJ, TC), literature review, and paper revision (LW, LY). All authors have made significant contributions to this study and have approved the final manuscript.

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