Liposomal irinotecan (Onivyde): Exemplifying the benefits of nanotherapeutic drugs

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Abstract
Irinotecan is a topoisomerase inhibitor, widely used in treatment of malignancies including pancreatic ductal adenocarcinoma (PDAC) as part of the FOLFIRINOX regimen prescribed as a first-line treatment in several countries. However, irinotecan has not been successfully introduced as a second-line treatment for pancreatic cancer and few randomized clinical studies have evaluated its added value. Efficacy of liposomal irinotecan (nal-IRI) combined with 5-fluorouracil and leucovorin (5-FU/LV) was reported in the phase III NAPOLI-1 trial in metastatic PDAC following failure of gemcitabine-based therapy. Several features of nal-IRI pharmacokinetics (PK) could result in better outcomes versus nonliposomal irinotecan. Irinotecan is a prodrug that is converted to active SN-38 by carboxylesterase enzymes and inactivated by cytochrome P450 3A4/3A5. SN-38 is inactivated by UGT1A1 enzymes. Individual variations in their expression and activity could influence enhanced localized irinotecan activity and toxicity. Liposomal irinotecan exploits the enhanced permeability and retention effect in cancer, accumulating in tumor tissues. Liposomal irinotecan also has a longer half-life and higher area under the concentration-time curve (0–∞) than nonliposomal irinotecan, as the liposomal formulation protects cargo from premature metabolism in the plasma. This results in irinotecan activation in tumor tissue, leading to enhanced cytotoxicity. Importantly, despite the longer exposure, overall toxicity for nal-IRI is no worse than nonliposomal irinotecan. Liposomal irinotecan exemplifies how liposomal encapsulation of a chemotherapeutic agent can alter its PK properties, improving clinical outcomes for patients. Liposomal irinotecan is currently under investigation in other malignancies including biliary tract cancer (amongst other gastrointestinal cancers), brain tumors, and small-cell lung cancer.

KEYWORDS
carcinoma, pancreatic ductal, chemotherapy, drug delivery system, irinotecan, liposome

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1 | INTRODUCTION

Liposomal carriers have been used to deliver anticancer drugs directly to tumors. Liposome deposition in tumors is thought to be facilitated by tumor blood vessel immaturity and leakiness, as well as by impaired lymphatic drainage at the tumor site (EPR). Reducing systemic drug exposure relative to tumor exposure in this manner might also improve safety. Examples include liposomal doxorubicin and nal-IRI (Onivyde® Servier (outside the USA and Taiwan; Les Laboratoires Servier SAS, 50 Rue Carnot, Suresnes 92284, France); Ipsen (within the USA; 106 Allen Road, Basking Ridge, NJ 07920, USA); PharmaEngine (Taiwan; 11F, 10 Minsheng East Road, Sec. 3, Taipei 104, Taiwan)).

Pancreatic ductal adenocarcinoma is a tumor with limited treatment options. Most patients present with metastatic disease at diagnosis and are ineligible for surgery. Advanced/metastatic pancreatic cancer is characterized by rapid clinical deterioration, thus chemotherapeutic treatment following progression on first-line therapy could be limited to palliative chemotherapy. Second-line treatment options remain limited and depend on the first-line treatment used. Liposomal irinotecan is an IV liposomal formulation that encapsulates the TOP1 inhibitor irinotecan in a lipid bilayer vesicle. Treatment with nal-IRI+5-FU/LV was associated with significantly improved outcomes for patients with mPDAC versus 5-FU/LV, including OS, median PFS, and ORR in the NAPOLI-1 study. Recent data have also shown improved PFS and OS outcomes for patients with biliary tract cancer receiving nal-IRI+5-FU/LV as second-line therapy.

We aim to provide an overview of the available PK data on nal-IRI, highlighting differences from nonliposomal irinotecan.

2 | IRINOTECAN AS AN ANTICANCER AGENT

In the US, irinotecan is indicated in first-line therapy for mCRC, with or without 5-FU/ LV, and in patients with recurrent or progressive disease following initial fluorouracil-based treatment. Irinotecan has shown activity in other cancer types. Clinical trial data for use of nonliposomal irinotecan as second-line therapy for PDAC after disease progression with gemcitabine-based treatment have shown varying degrees of activity.

2.1 | METABOLISM OF IRINOTECAN

2.1.1 | Irinotecan activation and inactivation

Nonliposomal irinotecan is a water-soluble prodrug that inhibits the TOP1 cation, mainly through its active metabolite SN-38, by stabilizing the TOP1/DNA complex, leading to DNA strand breaks, cell replication inhibition, and eventual cell death. SN-38 shows up to 1000-fold increased TOP1 inhibitory activity versus irinotecan (Figure 1). Irinotecan and its metabolites are excreted through a hepatobiliary pathway into the feces and urine by ABC transporters. The inactive SN-38 metabolite, SN-38G, can be reactivated to SN-38 by β-glucuronidases in the human colorectum. Increased levels of tumor β-glucuronidases could contribute to tumor SN-38 exposure in vivo.

2.1.2 | Individual variations in enzymes involved in irinotecan metabolism

Irinotecan response varies among patients, possibly due to variation in expression of enzymes involved in its elimination. Liver CYP3A4 levels vary depending on environmental, rather than genetic, factors. It is recommended to use CYP3A4 status (defined as 6/β-hydroxy cortisol / cortisol ratio) was found to be a predictor of diarrhea in patients with mCRC receiving a combination of irinotecan and 5-FU.

UGT1A enzymatic activity or expression levels show interpatient variability based on genetic predisposition. Examples include individuals with Gilbert’s syndrome who typically carry UGT1A1*28 promoter variants, or UGT1A1*, UGT1A7*, or UGT1A9*1b variants. These factors are typically associated with reduced SN-38 glucuronidation rates with nonliposomal irinotecan, with increased risk for gastrointestinal and bone marrow toxicities. UGT1A1*28 is predictive of neutropenia in patients with mCRC receiving nonliposomal irinotecan and 5-FU, and is associated with elevated plasma bilirubin.

Nonliposomal irinotecan-induced delayed-type diarrhea has been correlated with the presence of at least one UGT1A1*28 allele. UGT1A1*28 7/7 homozygosity is a risk factor for hematological toxicity in patients receiving irinotecan, depending on administration schedule.

UGT1A1*28 homozygosity also correlates with SN-38 concentrations in a nonliposomal irinotecan dose-dependent manner. UGT1A1*6 polymorphisms are observed in East Asians, but not in Caucasians. Glucuronidation activity of UGT1A1*6 is decreased to a similar extent as UGT1A1*28, and therefore, UGT1A1*6 is as important as UGT1A1*28 in East Asians. There are therefore gene-dose effects of UGT1A1*6 or *28 on glucuronidation activity, SN-38 exposure, and neutropenia, as the two polymorphisms are mutually exclusive. Although the effect of UGT1A1*28 on nonliposomal irinotecan toxicity was not suggested at lower doses in Caucasian patients, Asian patients harboring UGT1A1*6 or *28 experienced severe irinotecan toxicity at lower doses. It is recommended to reduce irinotecan dose for UGT1A1*6 or *28 homozygotes and those harboring both UGT1A1*6 and *28 or only one of these polymorphisms. Asian studies have focused on UGT1A1 polymorphism-associated toxicity. A study of 48 patients from China, including 8 with unresectable PDAC and 12 with unresectable biliary tract cancer receiving FOLFIRI or irinotecan monotherapy, used direct sequencing to identify UGT1A1*28*/6 polymorphisms. Patients homozygous or heterozygous for UGT1A1*6 polymorphisms were more likely to develop grade III/IV neutropenia versus patients with a WT
genotype. Patients heterozygous or homozygous for UGT1A1*6 and UGT1A1*28 polymorphisms were more likely to experience grade III/IV neutropenia versus patients with a double WT genotype.

The BioBank Japan project analyzed 651 patient records (102 cases and 549 controls of various malignancies), and found that UGT1A1*6 homozygosity was predictive of adverse irinotecan reactions. A meta-analysis of 1652 patient records from nine studies (eight from Asia) of patients with colorectal cancer associated UGT1A1*6 polymorphism with late-onset diarrhea and severe neutropenia. ABCB1 (P-glycoprotein) gene polymorphisms affect renal irinotecan clearance, with the ABCB1*8 genotype being independently associated with the irinotecan PK profile to a lesser extent than UGT1A1*28. One CES2 promoter region SNP that appears to result in decreased enzyme activity, and therefore decreased irinotecan activation, has been identified. Several SNPs identified in Japanese patients (1A>T; Met[1]Leu; 100 C>T, 424G>A, IVS8-2A>G) were found to reduce activity of CES2, either by reduced mRNA transcription or loss of enzyme activity.

3 | LIPOSOMAL IRINOTECAN

LIPOSOMAL IRINOTECAN (nal-IRI) consists of pegylated liposomal particles (111 nm diameter) encapsulating an irinotecan sucrosofate salt payload. The drug to
phospholipid ratio is 473 mg irinotecan-HCl/mmol phospholipid, and the phospholipid composition of the liposome is distearoylphosphatidylcholine, cholesterol, and pegylated 1,2-distearoyl-sn-glycerol-3-phosphoryl-etheranolamine in a molar ratio of 3:2:0.015. Liposomal encapsulation keeps irinotecan in circulation for longer before metabolic conversion to its active metabolite SN-38, leading to an improved pharmacokinetic profile. Approximately 95% of the irinotecan payload is retained within liposomes 24 h after nal-IRI administration, allowing for high drug load and increased plasma t1/2 versus nonliposomal irinotecan (Table 1). Analysis of patient-derived PDAC xenografts in immunocompromised mice has shown that nal-IRI has a higher therapeutic index than nonliposomal irinotecan (20 vs. 5) and prolongs time to reach tumor volume of 600 mm3 (90.5 vs. 60.6 days). Preclinical experiments using human histiocytic lymphoma cell lines (U937) indicated that TAMs, which express CES, can convert irinotecan to SN-38. Liposomal irinotecan appears to preferentially accumulate in tumor tissue through EPR, resulting in gradual accumulation in the tumor stroma. This results in continual SN-38 release through local TAM CES activity, as macrophages can take up nal-IRI liposomes, releasing their cargo and allowing access to CES enzymes. Tumor cells also express CES, and this CES might also be able to act on any irinotecan that has been locally released. Variability in PDAC CES expression could thus influence the response to irinotecan-based treatments. Conversely, nonliposomal irinotecan can be transported in and out of tissues with a short plasma t1/2, reducing SN-38 duration in tumors. Additionally, neutral plasma pH results in lactone ring opening, decreasing topoisomerase inhibition.

In preclinical human colon (HT-29) and breast (BT474) cancer xenograft models, nal-IRI showed superior efficacy versus nonliposomal irinotecan. In preclinical, ex vivo, time-course assays, nal-IRI conversion to SN-38 by nude mouse-derived macrophages required at least 24 h and was complete after 72 h. Nal-IRI showed significant and lasting tumor growth inhibition in a preclinical HT-29 mouse xenograft model versus nonliposomal irinotecan. Moreover, nal-IRI treatment resulted in longer intratumor SN-38 exposure and increased circulatory time in patient plasma compared with nonliposomal irinotecan, resulting in increased time above the tumor growth inhibition threshold. Computational PK modelling predicted that similar exposure of HT-29 mouse xenograft tumors to SN-38 from nal-IRI could be achieved at one-fifth of the dose versus nonliposomal irinotecan, with similar AUC, but longer tumor exposure above threshold and a higher efficacy (Table 2).

Similar effects have been seen in mouse xenograft models of breast cancer brain metastases.

### 3.1 Clinical PK properties of nal-IRI

Phase I PK data from patients with advanced solid tumors receiving nal-IRI (alone or with 5-FU/LV) showed a lower Cmax, prolonged t1/2, and higher SN-38 AUC (all in plasma) versus patients receiving nonliposomal irinotecan. Additionally, slow release of irinotecan from liposomes over time was suggested.

In a phase II study in patients with gastric cancer, the SN-38 t1/2 and AUC were increased with nal-IRI versus nonliposomal irinotecan, while a lower Cmax was maintained. Further analysis indicated that nal-IRI had a tIRI (sum of irinotecan in liposomes and free irinotecan) Cmax 13.4-times higher, a 1/2 2.0-times longer, and an AUC from time 0–∞ 46.2-times greater than nonliposomal irinotecan.

In a clinical trial that evaluated nal-IRI-mediated tumor delivery in biopsies collected 72 h following administration (70 mg/m2), tumor tIRI was 0.5-times higher than that observed in plasma. Tumor tSN-38 was 6-times higher than in plasma, and the tumor tSN-38 : tIRI (a measure of the extent of conversion) was 8-times higher than in plasma.

### 3.2 Liposomal irinotecan exposure–efficacy association

In the NAPOLI-1 nal-IRI+5-FU/LV arm, longer OS and PFS were associated with higher Cavg of tIRI, tSN-38, and uSN-38, as well as with longer time when SN-38 is above the threshold concentration of 0.03 ng/ml (tSN38>thr), with the strongest association noted for t1/2(uSN38>thr). In a population PK modelling analysis of nal-IRI using

| TABLE 1 Effects of the liposomal encapsulation of irinotecan in preclinical models |
|-----------------------------------------------|
| Advantage of nal-IRI encapsulation | Nonliposomal irinotecan | nal-IRI |
|-----------------------------------------------|
| Prolonged exposure in plasma | Irinotecan and SN-38 cleared from circulation within 8 h | Irinotecan and SN-38 remained in circulation within >50 h |
| Prolonged exposure in tumor xenograft models | >90% irinotecan cleared from tumors in 24 h; SN-38 exposure in tumors <48 h | Irinotecan persisted in tumors at >10,000 nmol/L for 168 h; prolonged SN-38 exposure above activity threshold for up to 168 h |
| Dose needed to achieve similar SN-38 exposure in plasma and tumors in xenograft models | 50 mg/kg | 10 mg/kg |
| Enhanced tumor growth inhibition in animal models | ~40% | ~110% |

Abbreviations: nal-IRI, liposomal irinotecan; SN-38, 7-ethyl-10-hydroxycamptothecin.
plasma samples from patients with various tumors (including colorectal, gastric, and pancreatic cancer) from six studies \((n = 353)\), higher \(C_{\text{avg}}\) and longer \(t_{\text{uSN38-thr}}\) was associated with longer OS and PFS in patients with PDAC receiving nal-IRI+5-FU/LV. This was also associated with an increased ORR; however, \(C_{\text{max}}\) was not associated with OS in these patients.\(^{55}\)

### 3.3 | Liposomal irinotecan exposure–safety association

In a phase II study in patients with mPDAC receiving nal-IRI, pharmacogenetic analysis of patient samples \((n = 28)\) for genetic polymorphisms in UGT1A1 and UGT1A9 did not find any correlation with toxicities, although the patient numbers are likely too small to identify any relationship.\(^ {56}\) In the NAPOLI-1 trial, of seven patients positive for the UGT1A1*28 polymorphism, five began treatment at a reduced starting dose and received the full planned dose of nal-IRI in subsequent treatment cycles.\(^ 4\)

A recent population PK analysis found that UGT1A1*28 was not a significant predictor of SN-38 levels following a nal-IRI dose, with the authors proposing that liposomal encapsulation lowered irinotecan release rate, avoiding increased plasma SN-38.\(^ {55}\) Additionally, a higher probability for neutropenia incidence and severity with higher uSN-38 \(C_{\text{max}}\) was observed. The association with neutropenia was stronger for uSN-38 \(C_{\text{max}}\) than for tSN-38 \(C_{\text{max}}\).\(^ 55\) It was also stronger for uSN-38 \(C_{\text{max}}\) than \(C_{\text{avg}}\). A higher incidence and severity of diarrhea was associated with higher tIRI \(C_{\text{max}}\). This effect was observed in Asian subpopulations but mostly in Caucasians. It is important to note that UGT1A1*6 polymorphism was not assessed, despite 42% patients in the study being of East Asian origin.

In NAPOLI-1, this association was only observed in the nal-IRI monotherapy arm, presumably due to the higher nal-IRI dose used \((100 \, mg/\text{m}^2 \text{ every 3 weeks vs. } 70 \, mg/\text{m}^2 \text{ every 2 weeks in the nal-IRI+5-FU/LV combination arm})\), resulting in higher tIRI \(C_{\text{max}}\) for patients receiving nal-IRI monotherapy.\(^ {4,55}\) Differences in observed neutropenia and diarrhea rates among Caucasian and Asian patients in NAPOLI-1 can be attributed to racial differences in the tIRI and uSN-38 \(C_{\text{max}}\), and potentially UGT1A1*6 genotypes that were not detected due to the study design.\(^ {55}\)

Japanese patients experienced more FOLFIRINOX (i.e., including nonliposomal irinotecan) related toxicities than Caucasian patients despite exclusion of patients homozygous for UGT1A1*28/*6 polymorphisms (or heterozygous for both).\(^ {57}\)

A phase II study of nal-IRI+5-FU/LV treatment in Japanese patients with mPDAC found no unexpected increases in rates of diarrhea or neutropenia versus the NAPOLI-1 trial.\(^ {58}\) Importantly, only three patients in the nal-IRI+5-FU/LV arm had relevant UGT1A1 mutations. The nal-IRI dose was the same in both this study and NAPOLI-1 \((80 \, mg/\text{m}^2, \text{equivalent to } 70 \, mg/\text{m}^2 \text{ irinotecan free base})\), however the nal-IRI dose was reduced for patients homozygous for UGT1A1*28 and UGT1A1*6 polymorphisms.

Dose modification did not significantly influence survival outcomes in a post-hoc analysis of patients from NAPOLI-1 who underwent protocol-specified dose modification; for example, OS with dose modification was 8.4 months versus 6.7 months without (hazard ratio 0.89; 95% confidence interval, 0.59–1.35),\(^ {59}\) suggesting nal-IRI dose modification is a feasible strategy to maintain clinical benefit. In Japan, dosing of nal-IRI is reduced according to UGT1A1 genotype\(^ {58}\), this aligns with the NAPOLI-1 study where patients homozygous for the UGT1A1*28 allele were initially treated with a 20 \(mg/\text{m}^2\) dose reduction of nal-IRI before building up to a full dose in the absence of any toxic effects.

### 3.4 | Potential for future clinical development of nal-IRI

The properties of nal-IRI have made it attractive for targeting various cancers. A retrospective study of 14 patients with metastatic biliary tract cancer showed that second-line treatment with nal-IRI+5-FU/LV resulted in half of the patients achieving disease control, suggesting efficacy in this population.\(^ {60}\) The phase II NIFET trial is currently underway, comparing use of nal-IRI+5-FU/LV with gemcitabine + cisplatin for treatment of locally advanced or metastatic biliary tract adenocarcinoma\(^ {61}\); the NALIRICC trial is also ongoing, comparing nal-IRI+5-FU/LV with 5-FU/LV in biliary tract cancer.\(^ {60}\) Data from the NIFTY trial have recently been presented, with improved OS and PFS outcomes for patients with biliary tract cancer receiving nal-IRI+5-FU/LV as a second-line treatment.\(^ {9}\) Data from preclinical models of small-cell lung cancer has shown that nal-IRI has antitumor activity at clinically relevant dose levels, with partial or complete responses observed in tumors derived from several cell line models, and improved survival outcomes in mouse models (vs. irinotecan and topotecan).\(^ {62}\) Liposomal irinotecan also had activity in the second-line setting following topotecan failure.\(^ {62}\)

Preclinical data from animal models of breast cancer brain metastases showed that liposomes preferentially accumulate in metastatic lesions after crossing the blood–brain barrier.\(^ {53}\) Moreover, nal-IRI treatment results in increased accumulation of both irinotecan and SN-38 in brain metastases. A phase I study of nal-IRI in 29 patients with metastatic breast cancer showed that patients with
central nervous system disease (n = 10) receiving nal-IRI had an ORR of 30%, indicating that nal-IRI could be a viable treatment option in this population. A phase I dose escalation study was carried out in patients with high-grade glioma, with WT UGT1A1 (n = 16) versus UGT1A1*28 heterozygotes (n = 18); this found a maximum tolerated nal-IRI dose of 120 mg/m² for WT, and 150 mg/m² for heterozygous patients, with nal-IRI safety and toxicity signals similar to previous observations. Further investigation will support understanding of potential nal-IRI activity in this context.

Expression profiling using a variety of human tumor tissue and liver samples showed that CES2 expression correlated with irinotecan conversion to SN-38. High CES2 expression levels in tumor tissue correlated with increased OS in patients with resectable and borderline resectable PDAC receiving neoadjuvant therapy with FOLFIRINOX (combination of irinotecan, 5-FU, oxaliplatin, and LV). High levels of CES activity in the small intestine suggest that irinotecan-associated delayed diarrhea is at least partly caused by local conversion of irinotecan to SN-38. A better understanding of CES2 levels could support individualized dosing of nal-IRI.

Cationic liposomes can stimulate dendritic cell activation in vitro, potentially by promoting expression of costimulatory molecules. This might create opportunities to combine liposomal formulations such as nal-IRI with immune checkpoint inhibitors. However, immune recognition of the liposomal formulation could result in clearance of the drug and therefore reduced delivery of the irinotecan payload.

4 CONCLUSION

The advent of liposomal agents such as nal-IRI has led to improvements in drug formulations with altered PK profiles compared with their parent compounds, which translate into different efficacy and safety profiles in clinical practice. Compared with nonliposomal irinotecan, nal-IRI generally shows increased exposure and prolonged retention (with a preference for accumulation in tumor cells), and has been shown to have increased plasma half-life among other desirable PK properties in multiple preclinical, in silico, and clinical studies. Ongoing refinement of delivery modes at the nano scale holds the promise that compounds with undesirable toxicity could become targetable at the tumor environment, reducing the incidence of negative off-target effects and improving efficacy.

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GM has received honoraria from Servier for advisory board meetings and conferences. FI holds a patent for UGT1A1 genotyping and is an Abbvie employee and stockholder. HM is an editorial board member of Cancer Science.

AUTHOR CONTRIBUTIONS

GM, FI, and HM contributed to the literature search, drafting the manuscript, and critically reviewing the content. GM, FI, and HM approved the final version of the manuscript for submission.

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