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Liposomal irinotecan for the treatment of metastatic pancreatic adenocarcinoma- A review

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Abstract
The second leading cause of death in the world is cancer. Out of all the cancers diagnosed Pancreatic cancer is the most deadly of all where the survival rate of 5 years is 9% when diagnosed at an early stage and only 2% survival rate when diagnosed at an advanced stage. The first line of treatment given to the patients is gemcitabine-based therapy. Liposomal irinotecan is designed for increasing the effectiveness of anti-tumor while reducing drug-related toxicity compared to the normal (non-liposomal) formation of this topoisomerase 1 inhibitor. In combination with 5-fluorouracil and leucovorin (5-FU / LV), nal-IRI the first agent to be specifically approved for use in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) has progressed following gemcitabine-based treatment. Nal-IRI plus 5-FU / LV has shown moderate efficiency and controlled toxicity of patients with mPAC previously treated with conventional chemotherapy with irinotecan. NAPOLI 1 Study that was conducted in more than 75 cities demonstrated an increase in overall survival rate (OS), progression-free survival (PFS), and a significant decrease in Hazard Ratio (HR).

Keywords: liposomal irinotecan, NAPOLI 1, leucovorin, 5- flurouracil, pancreatic cancer

Introduction
Pancreatic Ductal Adenocarcinoma at present stands as the 12 most prevalent cancer in the world. However, it is the fourth leading cause of carcinoma-related mortality [1].
The incidence rate reported in the Asian region is around 0.6/per 100,000 persons per year, which is relatively low as compared to the western region where the incidence rate is 12.6/per 100,000 persons per year. Therefore India also has a comparatively lower incidence of Pancreatic Ductal Adenocarcinoma. The Incidence rate in India ranges from 0.5 to 2.4/100,000 persons per year among women to 0.2 to 1.8/100,000 persons per year among men. The National Cancer Registry Programme (ICMR, Bengaluru) has estimated that by 2020, there will be 8440 and 6090 new cases of pancreatic cancer afflicting Indian men and women, respectively [2].
Globally, 458,918 new cases of pancreatic cancer have been reported in 2018, and 355,317 new cases are estimated to occur until 2040. Despite advancements in the detection and management of pancreatic cancer, the 5-year survival rate still stands at 9% only. Early detection may be the key to reducing mortality; however pancreatic cancer is mostly diagnosed in an advanced stage, and 80-90% of patients have unresectable tumors at the moment of diagnosis. Regardless of these recent advancements and multidisciplinary management, the 5-year survival rate of all-stage newly diagnosed pancreatic cancer was only 5-10% [3].
Preferred first-line treatment options for patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) include gemcitabine þ albumin-bound paclitaxel (gemcitabine/nab-paclitaxel) and non-liposomal irinotecan þ oxaliplatin þ 5-fluorouracil/leucovorin (5-FU/LV) (FOLFIRINOX). Both these treatment regimens are able to provide better survival outcomes compared to gemcitabine therapy setting new postoperative treatment options with good performance status. As there is utmost biological aggressiveness of pancreatic cancer and inadequate prognosis of patients, the constant search for novel preoperative systematic treatments to increase the long-term effectiveness of surgery [4].
Results from the NAPOLI-1 study (NCT01494506) demonstrated a survival benefit of liposomal irinotecan (ONIVYDE®, ONIVYDE pegylated liposomal; historical names include nal-IRI, MM-398, or PEP02) plus 5-fluorouracil and leucovorin (5-FU/LV) in patients with mPDAC previously treated with gemcitabine-based therapy [5].
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NAPOLI

NAPOLI1 was an international multicenter Phase 3 study conducted at 76 facilities in 14 countries between January 11, 2012 and September 11, 2013. In this study Patients aged 18 years and older with pancreatic adenocarcinoma with distant metastatic disease and pancreatic adenocarcinoma with recorded disease progression after previous gemcitabine-based therapy were included [7].

The efficacy of nal-IRI combined with 5-FU / LV in adult patients with mPDAC developed following gemcitabine-based treatment was evaluated in NAPOLI-1, anticipated, randomized, open-label, multicenter, national phase III clinical trial done. at 76 sites in 14 countries (Argentina, Australia, Brazil, Canada, Czech Republic, France, Germany, Hungary, Italy, South Korea, Spain, Taiwan, UK, and USA). Recently, the effectiveness of this combination has been evaluated in a few retrospectives, observational studies (evidence of real-world) from one or more institutions in Austria, Italy, South Korea, Taiwan, or the USA [4].

The results of the NAPOLI1 study (NCT01494506) showed liposomal irinotecan (ONIVYDE) historically known as nalIRI and 5 fluorouracil in patients who previously used mPDAC. It showed the life-prolonging effect of leucovorin (5FU / LV). Gemcitabine-based treatment treated [12]. Patients randomized to liposome irinotecan 5FU / LV in the NAPOLI1 trial had a median overall survival (OS) of 6.1 months, compared to 4.2 months in patients randomized to 5FU / LV. (hazard ratio [HR]: 0.67, 95% confidence interval [CI]: 0.49e0.92; P = 0.012) [12]. Median progression-free survival (PFS) was 3.1 months in patients assigned to liposome irinotecan® 5FU / LV, compared to 1.5 months in patients assigned to 5FU / LV. (HR: 0.56; 95% CI: 0.41e0.75, P = 0.0001) [7].

Liposomal Irinotecan vs Irinotecan

Liposomal irinotecan (NalIRI) is irinotecan hydrochloride encapsulated in the nanoliposomal drug delivery system (nanoliposomal irinotecan; nalIRI). Drug delivery technology represents a rational strategy for improving the pharmacokinetics and biodistribution of irinotecan while protecting it from premature metabolism. NalIRI uses a new intraliposomal drug stabilization technology to encapsulate irinotecan into long-term circulating liposome-based nanoparticles, resulting in high drug loading and high *in vivo* stability. The stable nanoliposomal formulation of irinotecan has several attributes that may provide an improved therapeutic index.

The controlled sustained release should enhance the activity of this schedule-dependent drug by increasing the duration of exposure of the tumor tissue to the drug. There are sensitive stages of the cell cycle. Improved pharmacokinetics and high intravascular retention of drugs in liposomes may result in site-specific drug delivery to solid tumors. Stroma targeting is due to the subsequent depot effect where liposomes accumulating in tumor-associated macrophages (TAMs) release drugs and locally convert it to the much more cytotoxic SN38. Preferably local bioactivation should reduce exposure to potential toxic sites and increase exposure to adjacent cancer cells within the tumor [8].

First-line treatment of metastatic pancreatic adenocarcinoma that is treated with gemcitabine regimens. Liposomal irinotecan and irinotecan are chemotherapeutic agents that can be given leucovorin and 5FU to treat metastatic pancreatic cancer. However, liposomal irinotecan and irinotecan are not compatible drugs due to their specific mechanism of action.

irinotecan, a cytotoxic alkaloid derivative of synthetic camptothecin, targets the topoisomerase I enzyme involved in DNA replication, transcription, and repair. The active metabolite of this drug, known as SN38, can cause 2 severe neutropenia, and cholinergic reactions that occur within 24 hours (eg, diarrhea, loss of appetite, immunosuppression). (Ipsen Biopharmaceuticals, 2017).

Irinotecan nanoliposomal formulation is a circulatory system (due to exposure to SN38) by increasing drug encapsulation and loading efficiency to prolong circulation and maintain sustained release time to enhance antitumor activity. Improves pharmacokinetic delivery by reducing gastrointestinal toxicity. Compared to irinotecan Liposomes irinotecan stay in the bloodstream for 11.7 hours and irinotecan stay in the bloodstream for 6.07 hours.

Advantages of choosing liposomal irinotecan over irinotecan include the ability to interfere with the widespread growth of dense fibrous tissue known as the fibrogenic response found in people with metastatic PDAC around the tumor [9].

Real-World Evidences

A comparative analysis has been done on the 3 studies performed on the population of the USA, Korea, and Taiwan. In all three studies, the impact of Liposomal Irinotecan has been investigated as a second-line treatment, outcomes, and its safety profile. In the study conducted by Barzi *et al* (2020) in the US, population investigations were done to understand the outcomes and dosing patterns of Liposomal Irinotecan. The findings of the study are presented in the table below.

Table 1

S. No	Study and Year	No. of Patients (N)	Treatment I- Line II/III- LinE		Progression free survival (PFS)	0verall survival (OS)	ECOG	Safety Profile	Dose Modification
1	Barzi *et al*, [10] 2020	257	nal-IRI (57%) and Gemcitabine	nal -IRI		Median OS from initiation of nal-IRI was 5.6 months (95% C], 4.8–7.3 months) for patients who received nal-IRI as first-line (n = 38) or second-line (n = 107) treatment (total n = 145) compared with 4.1 months (95% CI, 3.4–4.9 months) for patients treated with nal-IRI third line or later	The majority patients (110 patients) with I line nal -IRI had ECOG -1 and for those patients who got nal-IRI as II/III line treatment, the majority (101) had ECOG -1	18.7% of patients had neutropenia during their treatment with nal-IRI. Diarrhoea experienced by 46.3% patients. Only 4 patients had thrombocytopenia.	70 patients (27.2%) experienced at least 1 dose modification: 32.4% while receiving I/II line nal-IRI therapy plus 20.5% receiving nal-IRI third line or later. The median length of therapy for dose modified patients is 13.1 vs 6.1 weeks among patients without a dose modification
2	Su *et al*, [1] 2020	44	Gemcitabine	nal -IRI + 5 FU/LV	Median PFS was 2.5 months [95% CI]: 2.2-5.8 months)	The median OS was 6.6 months (95% CI: 3.8-9.5 months)	ECOG < 2	Around (43.2%) experienced neutropenia, 27.3% having grade 3-4 neutropenia. Grade 3 anemia in 37 and grade 4 anemia 15 patients. Thrombocytopenia not so common with only 22.7 % of incidence, 36.4% had ALT, Diarrhoea in 36.4% patients with no severe cases.	13.6 % patients had dose escalation and 20.6% HAD dose reduction
3	Park *et al*, [12] 2021	378	Gemcitabine	a. nal-IRI + 5FU/LV b. Folfirinox	a. The median PFS: 3.7 [95% confidence interval (CI): 2.3-5.1] months b. The median PFS- 4.6 (95% CI: 3.7-5.5) months	a. The median OS: 7.7 (95% CI: 5.6-9.8) b. The median OS - 9.7 (95% CI: 8.5-10.9)	a. ECOG Status- o and 1 b. ECOG status -2	All kinds of adverse events are more are more incident with FOLFIRINOX. than nal-IRI Grade 3-4 neutropenia -FOLFIRINOX (47.2%) vs -IRI/FL (35%). Grade 3-4 peripheral neuropathy FOLFIRINOX -5.9% Vs nal-IRI/FL - 1.0% Thrombocytopenia: FOLFIRINOX-17.3% Vs nal-IRI- 6.8% Peripheral Neuropahthy- FOLFIRINOX-34.7% Vs nal -IRI- 20.4%	More common in FOLFIRINOX 78.5% vs nal -IRI 33.7%

Adverse Drug Events

In the recent study conducted by Wainberg *et al*, each of the 32 patients experienced adverse events. Most common being grade 3 neutropenia (10 patients), febrile neutropenia (4 patients), grade 3 diarrhea (4 patients) and thromboembolic events (5 patients). Other prevalent adverse Reactions that were observed are hypokalaemia and alanine aminotransferase increase [5].

In another study conducted by Glassman *et al*., many patients reported grade 3, grade 4 neutropenia, nausea, anemia, vomiting, and fatigue.Yoo *et al*. also witnessed parallel adverse drugs.Effects include nausea, vomiting, and fatigue [11].

As per a study conducted by Barzi *et al* about 18.7% complained of neutropenia of all grades during the treatment with nal-IRI. Apart from neutropenia diarrhea was also reported in about 46% of the patients undergoing treatment. Thrombocytopenia was only reported in 4% of the patients undergoing treatment [10].

According to the NAPOLI study neutropenia and diarrhea were found to be the most common type of TEAE. Some patients also suffered from grade3-4 neutropenic sepsis. Neutropenia and diarrhea usually appeared in the early treatment phases. In 62% of the patients, TEAE has led to withholding of the nal-IRI + 5FU/LV.Around 33% of patients had to get dose reduction due to tolerability issues. While only 11% of patients went for treatment termination caused by TEAE, only 1 death was reported in this group.

The tolerability of NAPOLI 1 was found to be somewhat congruent with the studies conducted in the East Asian region. The most common type of adverse events observed in South Korean study populations was nausea, vomiting, neutropenia, and diarrhea. While for Taiwanese study population the most prevalent ADR reported was grade 3-4 neutropenia. Neutropenia was observed to be the main cause of dose modification.

Conclusion

Liposomal Irinotecan is the most advanced drug used in the treatment of pancreatic cancer. Combined with 5-FU / LV, liposomal irinotecan is the first direct authorization agent such as the treatment of advanced metastatic pancreatic cancer following gemcitabine-based therapy of countries, including the USA and the EU (LAMB)

OS benefits from nal-IRI + 5-FU / LV over 5-FU / LV alone is seen in many pre-and post-test tests subgroup analyzes patient, tumor and previous treatment features at first, a very noticeable contrast in patients previously exposed to common irinotecan.

Some study recommends the use of premature dose to reduce or delay the associated toxicity control strategy. There was no significant effect on the survival effects within the arm of the liposomal irinotecanþ5-FU / LV among patients requiring tolerant-directed dose adjustment and those who did not. Consistent with the results reported in NAPOLI1, OS and PFS were significantly higher in patients who received liposomal irinotecanþ5-FU / LV also requires timely dose adjustment (dosage reduction or delay) compared to those who received 5-FU / LV.

Patients receiving liposomal treatment irinotecanþ5-FU / LV once their caregivers should be aware of management strategies TEAEs are toxic, including dose modification. (64)

Liposomal treatment irinotecan5-FU / LV too improved OS and PFS compared to 5-FU / LV in NAPOLI-1 research and demonstrated controllable safety and tolerance profile.

Treatment with liposomal irinotecan along with 5FU/LV enhanced the overall survival rate and progression-free survival compared with 5FU/LV in the Napoli study. Apart from this liposomal irinotecan along with 5FU/LV showed greater safety and improved tolerability. (64)

The analysis suggests the use of premature dose reducing or delaying the associated toxicity control strategy Treatment of liposomal irinotecanþ5-FU / LV may not be adverse clinical results. There was no significant effect on the survival effects within the arm of the liposomal irinotecanþ5-FU / LV among patients requiring tolerant-directed dose adjustment and those who did not. Consistent with the results reported in NAPOLI1, OS and PFS were significantly higher in patients who received liposomal irinotecanþ5-FU / LV also requires timely dose adjustment (dosage reduction or delay) compared to those who received 5-FU / LV.

Patients receiving liposomal treatment irinotecanþ5-FU / LV once their caregivers should be aware of management strategies TEAEs are toxic, including dose modification. (64)

In conclusion, nal-IRI, combined with 5-FU / LV, is the first type and is specially approved for use as the second- or next-line treatment in patients preceded by gemcitabine with mPDAC and, thus, represents an important treatment option.

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