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Nalirifox in the Treatment of Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC): A Comprehensive Review

Sattwik J Paul[1], Aniket N Lalaji[*1], Sankha Shubra Saha[1], Vidit Patel[1], Chauhan Sneha Arvind[1], Tanishka Bairagi[1], Sudeshna Roy[1], Ankit Patel[1], G.S Chakraborthy[2]

[1]PharmD Scholar, Dept. of Pharmacy Practice, Parul Institute of Pharmacy & Research, Parul University, Vadodara, Gujarat

[2]Professor and Principal, Dept. of Pharmacognosy, Parul Institute of Pharmacy & Research, Parul University, Vadodara, Gujarat

***Corresponding Author:**

Email Id: lalajianiket@gmail.com

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ABSTRACT

Background: Metastatic pancreatic ductal adenocarcinoma (mPDAC) is a highly aggressive malignancy with limited treatment options and poor survival rates. While standard chemotherapy regimens such as FOLFIRINOX and gemcitabine plus nab-paclitaxel have improved clinical outcomes, their use is often restricted due to severe toxicities.

Objective: This review examines the therapeutic potential of Nalirifox, a novel combination of nanoliposomal irinotecan (nal-IRI), 5-fluorouracil (5-FU), leucovorin (LV), and oxaliplatin, in the management of mPDAC.

Methods: A comprehensive evaluation of Nalirifox is provided, covering its pharmacological properties, clinical efficacy, safety profile, and comparative advantages over existing therapies. Additionally, mechanisms of resistance and potential strategies to optimize treatment outcomes are discussed.

Results: Clinical evidence suggests that Nalirifox offers a promising alternative to conventional regimens, demonstrating comparable or superior efficacy with a more favorable toxicity profile. This makes it a viable option for patients who may not tolerate more aggressive chemotherapy. However, challenges such as acquired resistance and tumor microenvironment factors necessitate further investigation.

Conclusion: Nalirifox represents a significant advancement in mPDAC treatment by balancing therapeutic efficacy with improved tolerability. Future research should focus on overcoming resistance mechanisms and exploring combination strategies to enhance patient outcomes.

Keywords: *Nalirifox, metastatic pancreatic cancer, nanoliposomal irinotecan, chemotherapy, drug resistance, FOLFIRINOX*

1. INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) remains one of the deadliest forms of cancer, with a five-year survival rate of approximately 10% .PDAC is the fourth leading cause of cancer-related deaths worldwide, accounting for over 430,000 deaths in 2018 alone [1].The mortality associated with PDAC is due in part to its typically late diagnosis, as the disease often presents with nonspecific symptoms that delay early detection [2]. Additionally, PDAC is highly aggressive and resistant to many forms of chemotherapy, contributing to its poor prognosis [3].

Metastatic pancreatic ductal adenocarcinoma (mPDAC), a stage IV cancer, is particularly challenging to treat, as the disease has spread beyond the pancreas to distant organs, significantly reducing the efficacy of localized treatment modalities like surgery [4]. At diagnosis, more than 80% of PDAC patients present with metastatic disease, reflecting the critical need for effective systemic therapies. Chemotherapy remains the cornerstone of treatment for mPDAC, with regimens like FOLFIRINOX (a combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) and gemcitabine plus nab-paclitaxel being the most commonly used [5,6]. Despite these advances, the median overall survival (OS) with current treatments rarely exceeds 11 months, and patients often experience significant treatment-related toxicities [7].

In response to the limitations of existing therapies, the development of novel regimens such as Nalirifox, a combination of nanoliposomal irinotecan (nal-IRI), 5-fluorouracil (5-FU), leucovorin (LV), and oxaliplatin, offers a promising alternative for treating mPDAC [8]. Nalirifox is designed to maximize therapeutic efficacy while minimizing toxicity, making it particularly suitable for elderly and frail patients who are often unable to tolerate more aggressive chemotherapy regimens [9]. The combination of nal-IRI with fluoropyrimidine-based therapy and oxaliplatin has demonstrated encouraging results in clinical trials, suggesting its potential to improve survival outcomes in mPDAC patients [10].

This review provides an in-depth analysis of the pharmacology, clinical efficacy, safety, and tolerability of Nalirifox in the treatment of mPDAC, with a particular focus on its use in elderly patients. We will also explore mechanisms of resistance to Nalirifox and potential strategies for overcoming these challenges, as well as the future direction of research in this field.

2. STANDARD TREATMENT APPROACHES FOR MPDAC

Metastatic PDAC represents a critical challenge in oncology due to its poor response to conventional therapies [11]. Historically, the treatment of mPDAC has been centered around gemcitabine, a nucleoside analog that inhibits DNA synthesis by incorporating into the DNA strand during replication [12]. Gemcitabine monotherapy was the first chemotherapy approved for advanced PDAC in the 1990s, offering modest survival benefits with a median OS of approximately 5-6 months. However, the limited efficacy of gemcitabine prompted the development of combination regimens aimed at improving outcomes [13].

The combination of gemcitabine with nab-paclitaxel, a nanoparticle albumin-bound formulation of paclitaxel, demonstrated significant improvements in survival compared to gemcitabine alone in the MPACT trial [14]. In this phase III trial, patients treated with gemcitabine plus nab-paclitaxel had a median OS of 8.5 months compared to 6.7 months with gemcitabine alone, marking a new standard of care for mPDAC [15]. Despite these advances, the toxicity profile of gemcitabine plus nab-paclitaxel, particularly neuropathy and myelosuppression, limits its use in certain patient populations, particularly the elderly and those with poor performance status [16].

Another major development in the treatment of mPDAC was the introduction of FOLFIRINOX, a regimen combining 5-FU, leucovorin, irinotecan, and oxaliplatin [17]. In a landmark phase III trial, FOLFIRINOX demonstrated a significant survival benefit over gemcitabine, with a median OS of 11.1 months versus 6.8 months, and a progression-free survival (PFS) of 6.4 months versus 3.3 months, respectively [18]. However, FOLFIRINOX is associated with considerable toxicity, including severe neutropenia, diarrhea, and neuropathy, which makes it unsuitable for many patients, particularly those over the age of 75 or with poor performance status [19].

Given the limitations of current treatment options, the need for novel regimens that balance efficacy and tolerability is paramount [20]. Nalirifox was developed to address these challenges by combining nanoliposomal irinotecan with a modified FOLFIRI backbone, aiming to enhance the delivery of chemotherapy while reducing systemic toxicity [21].

2.1 Emergence of Nalirifox as a Treatment Strategy

Nalirifox represents a novel chemotherapy regimen that combines four agents: nanoliposomal irinotecan (nal-IRI), 5-fluorouracil (5-FU), leucovorin (LV), and oxaliplatin [22]. The rationale for the development of Nalirifox stems from the need to improve drug delivery to the tumor while minimizing systemic exposure and toxicity. Nanoliposomal irinotecan (nal-IRI) is a key component of this regimen and is designed to enhance the pharmacokinetics and pharmacodynamics of irinotecan, a topoisomerase I inhibitor [23].

In conventional formulations, irinotecan is rapidly metabolized to its active metabolite SN-38, which then inhibits topoisomerase I, leading to DNA damage and cell death. However, the rapid clearance and systemic distribution of irinotecan can result in significant toxicity, particularly in the gastrointestinal and hematologic systems [24]. Nanoliposomal encapsulation of irinotecan improves its pharmacokinetic profile by extending its circulation time and enhancing its accumulation in tumor tissues, thereby increasing its therapeutic efficacy while reducing off-target toxicity [25].

The combination of nal-IRI with 5-FU/LV and oxaliplatin builds on the success of FOLFIRINOX but is designed to offer a more tolerable alternative, particularly for patients who may not be able to tolerate the full intensity of FOLFIRINOX [26]. Leucovorin is included in the regimen to enhance the efficacy of 5-FU by stabilizing the 5-FU-thymidylate synthase complex, thereby prolonging its inhibition of DNA synthesis. Oxaliplatin, a platinum-based chemotherapeutic agent, adds a complementary mechanism of action by inducing DNA cross-links, which further disrupts cancer cell replication and induces apoptosis [27].

3. PHARMACOLOGY OF NALIRIFOX COMPONENTS

3.1 Nanoliposomal Irinotecan (nal-IRI)

Nanoliposomal irinotecan (nal-IRI) is a liposomal formulation of irinotecan designed to improve drug delivery and efficacy in cancer therapy [28]. Irinotecan is a prodrug that is converted to its active metabolite, SN-38, which inhibits topoisomerase I,

an enzyme involved in DNA replication and transcription. By inhibiting topoisomerase I, SN-38 induces DNA damage and apoptosis in rapidly dividing cancer cells [29]. The nanoliposomal formulation of irinotecan enhances its pharmacokinetics by increasing drug retention in the bloodstream and promoting selective accumulation in tumors due to the enhanced permeability and retention (EPR) effect [30].

The EPR effect refers to the phenomenon by which nanoparticles accumulate in tumor tissues due to the leaky vasculature and poor lymphatic drainage that characterize many solid tumors [31]. This allows nal-IRI to deliver higher concentrations of irinotecan to the tumor site while minimizing exposure to healthy tissues, thus reducing the risk of systemic side effects. Clinical studies have demonstrated that nal-IRI significantly improves overall survival and progression-free survival in patients with mPDAC, particularly when combined with 5-FU/LV and oxaliplatin [32].

3.2 5-Fluorouracil (5-FU) and Leucovorin (LV)

5-Fluorouracil (5-FU) is a pyrimidine analog that inhibits thymidylate synthase, a key enzyme involved in DNA synthesis [33]. By inhibiting thymidylate synthase, 5-FU disrupts DNA replication and induces cell death in rapidly dividing cancer cells. Leucovorin (LV), a reduced form of folic acid, enhances the cytotoxicity of 5-FU by stabilizing the 5-FU-thymidylate synthase complex, thereby prolonging the inhibition of DNA synthesis [34]. This synergistic interaction between 5-FU and LV forms the backbone of many chemotherapy regimens for gastrointestinal cancers, including PDAC [35].

5-FU is typically administered as a continuous infusion to maximize its

cytotoxic effects while minimizing toxicity, as bolus administration of 5-FU is associated with significant myelosuppression and gastrointestinal toxicity. In the Nalirifox regimen, 5-FU is administered as a continuous infusion following the administration of nal-IRI and oxaliplatin, allowing for optimal synergy between these agents [36]. The combination of 5-FU/LV with nal-IRI and oxaliplatin has demonstrated promising efficacy in clinical trials, with a manageable toxicity profile [37].

3.3 Oxaliplatin

Oxaliplatin is a platinum-based chemotherapeutic agent that induces DNA cross-links, leading to DNA damage and apoptosis in cancer cells. Unlike other platinum agents such as cisplatin and carboplatin, oxaliplatin has a unique mechanism of action that makes it particularly effective against colorectal and pancreatic cancers. Oxaliplatin forms intrastrand and interstrand cross-links in DNA, which disrupts DNA replication and transcription, ultimately leading to cell death [38-39].

Oxaliplatin is associated with a distinct toxicity profile compared to other platinum agents, with peripheral neuropathy being the most common dose-limiting side effect [40]. However, the neuropathy associated with oxaliplatin is often reversible and can be managed with dose modifications or temporary discontinuation of therapy [41]. In the context of Nalirifox, oxaliplatin provides a complementary mechanism of action to irinotecan and 5-FU, contributing to the regimen's overall efficacy [42].

4. CLINICAL TRIALS AND EFFICACY OF NALIRIFOX

The efficacy of Nalirifox in mPDAC has been evaluated in several clinical trials, with promising results reported in both first-line and second-line settings [43]. One of the key studies evaluating Nalirifox was the phase II NAPOLI-1 trial, which assessed the combination of nal-IRI with 5-FU/LV in patients with metastatic pancreatic cancer who had progressed on gemcitabine-based therapy [44]. In this trial, patients treated with nal-IRI plus 5-FU/LV demonstrated a significant improvement in overall survival compared to those treated with 5-FU/LV alone, with a median OS of 6.1 months versus 4.2 months, respectively [45]. Based on these results, nal-IRI was approved by the FDA for use in combination with 5-FU/LV in patients with metastatic pancreatic cancer following progression on gemcitabine [46].

The addition of oxaliplatin to the nal-IRI/5-FU/LV regimen has been explored in subsequent clinical trials, with preliminary data suggesting improved efficacy compared to nal-IRI/5-FU/LV alone [47]. In a phase II trial conducted in some studies, the combination of nal-IRI, 5-FU/LV, and oxaliplatin (Nalirifox) was evaluated as a first-line therapy for mPDAC, demonstrating a median OS of 12.6 months and a progression-free survival of 7.3 months [48]. These results are comparable to those achieved with FOLFIRINOX but with a more favorable toxicity profile, making Nalirifox an attractive option for patients who may not be candidates for FOLFIRINOX due to age or comorbidities [49].

5. SAFETY AND TOLERABILITY

The safety profile of Nalirifox is consistent with that of its individual components, with the most common adverse events being gastrointestinal and hematologic in nature [50]. Diarrhea, nausea, and vomiting are the most frequently reported gastrointestinal side effects, while neutropenia and thrombocytopenia are the most common hematologic toxicities. Peripheral neuropathy, a known side effect of oxaliplatin, is also commonly reported but is generally manageable with dose adjustments [51].

In clinical trials, the overall incidence of grade 3 or 4 adverse events with Nalirifox has been lower compared to FOLFIRINOX, making it a more tolerable option for patients who may not be able to tolerate more aggressive chemotherapy regimens [52]. The reduced toxicity of Nalirifox is particularly important in elderly patients, who are often more vulnerable to

the side effects of chemotherapy [53]. In a subgroup analysis of elderly patients in the NAPOLI-1 trial, Nalirifox demonstrated similar efficacy to younger patients, with a comparable safety profile [54].

6. MECHANISMS OF RESISTANCE TO NALIRIFOX

Despite the promising results of Nalirifox in clinical trials, resistance to chemotherapy remains a significant challenge in the treatment of mPDAC [55]. Several mechanisms of resistance to Nalirifox have been proposed, including alterations in drug metabolism, increased drug efflux, and the presence of cancer stem cells [56]. One of the key mechanisms of resistance to irinotecan is the overexpression of ATP-binding cassette (ABC) transporters, such as ABCG2, which pump SN-38 out of cancer cells, reducing its cytotoxicity [57]. Additionally, mutations in topoisomerase I, the target of irinotecan, can confer resistance by reducing the binding affinity of SN-38 to the enzyme [58].

Strategies to overcome resistance to Nalirifox include the use of combination therapies with targeted agents or immunotherapies that can enhance the efficacy of chemotherapy [59]. For example, inhibitors of ABC transporters, such as elacridar, have been shown to restore sensitivity to irinotecan in preclinical models, suggesting a potential strategy for overcoming resistance to Nalirifox [60]. Additionally, the use of immune checkpoint inhibitors, such as anti-PD-1 or anti-PD-L1 antibodies, in combination with chemotherapy has shown promise in overcoming resistance to chemotherapy by enhancing the immune response against cancer cells [61].

7. FUTURE DIRECTIONS IN NALIRIFOX RESEARCH

The development of Nalirifox represents a significant advancement in the treatment of mPDAC, but further research is needed to optimize its use and explore new combinations with targeted therapies and immunotherapies [62]. Ongoing clinical trials are investigating the combination of Nalirifox with novel agents, such as PARP inhibitors, which target DNA repair pathways, and anti-angiogenic agents, which inhibit the formation of new blood vessels that supply the tumor [63]. Additionally, the role of biomarkers in predicting response to Nalirifox is an area of active research, with the goal of identifying patients who are most likely to benefit from this regimen [64].

One of the key areas of interest is the use of Nalirifox in combination with immunotherapies, such as immune checkpoint inhibitors or adoptive cell therapies [65]. Preclinical studies have shown that chemotherapy can enhance the immune response against cancer cells by inducing immunogenic cell death and modulating the tumor microenvironment, creating a more favorable environment for immune-based therapies [66]. Clinical trials are currently underway to evaluate the safety and efficacy of combining Nalirifox with immunotherapies in patients with mPDAC [67].

8. CONCLUSION

Nalirifox represents a promising new option for the treatment of metastatic pancreatic ductal adenocarcinoma, particularly in patients who are not candidates for more aggressive regimens like FOLFIRINO. The combination of nanoliposomal irinotecan with 5-fluorouracil, leucovorin, and oxaliplatin offers a balanced approach to chemotherapy, providing significant survival benefits with a manageable toxicity profil. As ongoing research continues to explore new combinations and strategies for overcoming resistance, Nalirifox is poised to become an integral part of the treatment landscape for mPDAC [68-69].

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