Pancreatic Cancer Treatment by Nab-Paclitaxel with Gemcitabine Combination

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Pancreatic cancer has one of the highest mortality rates among cancers, and a combination of nab-paclitaxel with gemcitabine remains the cornerstone of first-line therapy. Nab-paclitaxel with gemcitabine in combination with other therapeutic agents can be new treatment strategies in pancreatic cancer. Seven therapeutic agents (ibrutinib, necuparanib, tarextumab, apatorsen, cisplatin, enzalutamide, and momelotinib) are found.

Keywords: pancreatic cancer ; pancreas adenocarcinoma ; drug combination ; paclitaxel ; gemcitabine ; cancer ; PDAC ; adverse effects ; clinical trial

1. Introduction

Pancreatic cancer continues to present challenges that have yet to be resolved by state-of-the-art medicine. The worldwide incidence of pancreatic cancer among men (5.7 per 100,000 people) is higher than that among women (4.1 per 100,000 people). This type of cancer is also the seventh leading cause of cancer death in both sexes and is more deadly in men (4.9 per 100,000 people) than in women (4.5 per 100,000 people) [1][2][3][4][5]. Adenocarcinoma of the exocrine pancreas represents 90% of pancreatic cancer cases, and its most widely accepted classifications are resectable, borderline resectable, and locally advanced pancreatic cancer [6][7]. The staging system used most often for pancreatic cancer is the TNM (tumor/node/metastasis) system from the American Joint Committee on Cancer (8th edition) [7][8][9][10][11]. Depending on the location of the tumor, most patients become symptomatic late in the disease. Consequently, patients with previously untreated advanced pancreatic ductal adenocarcinoma, who represent 50–55% of cases [7], have a very short life expectancy [12]. Therefore, efforts are currently being made to improve the diagnosis and treatment of this disease [13].

Recently, advances have been made to detect metastatic pancreatic ductal adenocarcinoma (PDAC) using molecular magnetic resonance imaging (MMRI) [14]. Additionally, advances have been made in liquid biopsy [15] and in finding specific biomolecular or subcellular targets [16][17][18][19], new therapeutic agents [20], and nanomedicine applications [21][22][23][24][25][26][27][28]. Moreover, the understanding of the molecular biology events of pancreatic cancer cells has increased [29][30][31]. At present, gemcitabine plus nab-paclitaxel is the preferred treatment for patients with pancreatic cancer [32][33][34][35]. Several research groups proposed complementing this treatment with other therapeutic agents seeking greater efficacy and safety. The advent of a therapy that decreases adverse events and improves overall survival outcomes in pancreatic cancer patient populations will be a milestone in medical research.

Currently, the indicated treatment is based on the stage and health status of the patient. Despite efforts to advance targeted therapy, immunotherapy [36], and nanomedicine [21][25], chemotherapy remains one of the most important therapeutic options, especially in PDAC. Over the last 30 years, treatment of PDAC has been improved from standard chemotherapies, consisting of fluoropyrimidines such as 5-FU and the antimetabolite drug gemcitabine, to new drug combinations. Adjuvant chemotherapy (after surgery) is the current method of care used for those with resectable pancreatic cancer, where gemcitabine as the single agent has a benefit in patient survival, particularly for those who have a limited functional state. However, regimens with multiple agents provide survival advantages, including gemcitabine plus capecitabine and FOLFIRINOX (fluorouracil, folinic acid, irinotecan, and oxaliplatin), which improves the disease-free survival over that with gemcitabine alone. However, this treatment is associated with higher toxicity [37][38].

The use of chemotherapy before surgery (neoadjuvant) to treat resectable cancer has uncertain benefits, but neoadjuvant chemotherapy has become the standard of care for some diseases, such as borderline resectable, locally advanced, and metastatic cancer. Locally advanced and metastatic diseases are treated with FOLFIRINOX or nab-paclitaxel with gemcitabine (NP/G). NP/G has shown good results in overall survival compared with gemcitabine monotherapy. In addition, progression-free survival and objective response rates were also improved [39][40][41]. Furthermore, when the

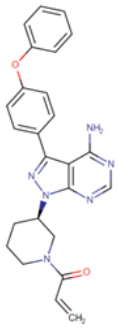
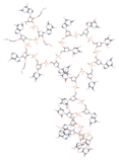
efficacy and safety of NP/G and FOLFIRINOX were compared, the response rate was shown to be 6.3% in the FOLFIRINOX group and 40.9% in the NP/G group; drug toxicity in the NP/G group was also less than that in the FOLFIRINOX group [41].

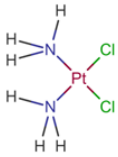
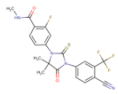
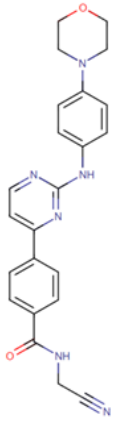
Gemcitabine is a nucleoside analog of deoxycytidine and inhibits the progression of cells found in the G1/S phase. The intracellular uptake of gemcitabine is mediated mainly by nucleoside transporters (ENTs), while the unidirectional transport of nucleosides into cells is mediated by the family of concentrative nucleoside transporters (CNTs). For many years, gemcitabine monotherapy remained the gold standard of treatment for advanced PDAC. Then, abraxane and albumin-bounded paclitaxel nanoparticles (nab-paclitaxel) in combination with gemcitabine (NP/G) emerged as a new method of treatment for patients with metastatic pancreatic cancer [42]. Nab-paclitaxel was approved in 2013 for advanced-stage pancreatic cancer [43]. Paclitaxel is a widely used and successful natural antineoplastic drug that acts by stabilizing microtubules (polymers composed of repeated subunits of α- and β-tubulin heterodimers), increasing cell polymerization and stopping the cell cycle in the G2/M phase, which leads to cell death [40][44][45]. A combination of paclitaxel and other therapeutic agents was also shown to be effective, e.g., when used with palbociclib in triple-negative breast cancer (TNBC) [46]. Nab-paclitaxel is a formulation of paclitaxel with albumin that is synthetized via the homogenization of serum albumin at a concentration from 3 to 4%, with paclitaxel added to improve the drug's biodistribution [44].

2. Pancreatic Cancer Treatment by Nab-Paclitaxel with Gemcitabine Combination

Table 1 shows the diversity of therapeutic agents under investigation in clinical trials. Considering the diversity in the chemical structures of the therapeutic agents enlisted, molecular biology studies will likely be needed to relate cellular or molecular events with the responses of patients to the triple regimen.

Table 1. Summary of treatment regimens for patients with previously untreated advanced pancreatic ductal adenocarcinoma (PDAC).

Ref	Therapeutic Agent	Structure	Description
[47]	Ibrutinib		**Ibrutinib is a Bruton's tyrosine kinase inhibitor that forms a covalent bond with a cysteine residue (Cys 481). Ibrutinib is used to treat chronic lymphocytic leukemia, mantle cell lymphoma, and Waldenstrom's macroglobulinemia, leading to inhibition of BTK activity [48][49].** **ClinicalTrials.gov identifier: NCT024366. Phase III RESOLVE study. Ibrutinib plus nab-paclitaxel/gemcitabine did not improve OS or PFS for patients with metastatic PDAC.**
[50]	Necuparanib	—	**Necuparanib (a heparin mimetic) acts as a multitargeting therapeutic, altering multiple signaling pathways simultaneously by binding and sequestering different proteins [51][52].** **ClinicalTrials.gov identifier: NCT01621243. A randomized phase II trial. Necuparanib plus nab-paclitaxel/gemcitabine did not improve OS.**
[53]	Tarextumab	—	**Monoclonal antibodies (mAb, anti-Notch2/3, OMP-59R5) are fully human monoclonal antibodies that target the Notch2 and Notch3 receptors. They have been used in trials studying the treatment of solid tumors, stage IV pancreatic cancer, and stage IV small cell lung cancer [54][55].** **ClinicalTrials.gov identifier: NCT01647828. A randomized phase II trial.** **Tarextumab plus nab-paclitaxel/gemcitabine did not improve OS, PFS, or ORR in first-line metastatic PDAC**
[56]	Apatorsen		**Apatorsen is a second-generation antisense drug in preclinical experiments that inhibits the production of heat shock protein 27 (Hsp27), a cell survival protein found at elevated levels in many human cancers, including prostate, lung, breast, ovarian, bladder, renal, pancreatic, multiple myeloma, and liver cancer [57][58].** **ClinicalTrials.gov identifier: NCT01844817. A randomized, double-blinded, phase II trial. The RAINIER trial. Addition of apatorsen to nab-paclitaxel/gemcitabine regimen did not improve survival or other clinically relevant endpoints in patients with metastatic pancreatic cancer.**

Ref	Therapeutic Agent	Structure	Description
[59]	Cisplatin		Cisplatin is a platinum-based chemotherapy agent used to treat various sarcomas, carcinomas, lymphomas, and germ cell tumors. Cisplatin exerts its anticancer activities by generating DNA lesions through interactions with purine bases, leading to the activation of various signal transduction pathways leading to apoptosis [60][61][62]. ClinicalTrials.gov identifier: NCT01893801. A nonrandomized phase 1b/2 pilot clinical trial. The addition of cisplatin to nab-paclitaxel/gemcitabine resulted in a high response rate and evolving OS.
[63]	Enzalutamide		Enzalutamide is a rationally designed, targeted androgen-receptor inhibitor used to treat castration-resistant prostate cancer. Enzalutamide acts both by inhibiting the translocation of the androgen receptor into the nucleus and by reducing the transcriptional activity of this receptor [64][65]. ClinicalTrials.gov identifier: NCT02138383. A phase I trial. Enzalutamide plus nab-paclitaxel/gemcitabine was safely administered with no unexpected toxicities and resulted in consistent reductions in CA 19–9 (biological marker) levels.
[66]	Momelotinib		Momelotinib is a benzamide that acts as an ATP-competitive JAK1/JAK2 inhibitor. Momelotinib has been used in trials studying the treatment of polycythemia vera, primary myelofibrosis, post-polycythemia vera, essential thrombocythemia, and primary myelofibrosis (PMF), among others [67][68]. ClinicalTrials.gov identifier: NCT02101021. Phase 1 dose-escalation study. Momelotinib plus nab-paclitaxel/gemcitabine was safe and well tolerated, with no OS or PFS benefits.

The molecular effects of paclitaxel, gemcitabine, and cisplatin are well characterized in cancer cells [69][70][71][72][73][74][75][76][60]. However, a successful triple regimen whose cellular events are known with certainty will bring about a new paradigm for the treatment of pancreatic cancer. Clinical trials of combination therapies that are effective and safe should be complemented by molecular studies to understand the pathways for their biological activities.

The MPACT, a randomized phase III study, reported that NP/G had an OS of 8.5 months, a PFS of 5.5 months, a CR of less than 1%, and an RP of 23% in 431 patients, resulting in greater efficacy than gemcitabine monotherapy. The AE of third grade or higher were as follows: neutropenia (38%), fatigue (17%), and neuropathy (17%). Febrile neutropenia was also present in 3% of the patients [77], whereas in [47][53][56], placebo in combination with the NP/G regimen exceeded the formulation of the main regimen with the additional drug in ORR, OS, and PFS, which means that adding ibrunitib (Bruton's tyrosine kinase inhibitor), tarextumab (IgG2 antibody against Notch2 and Notch3 receptors), or apatorsen (antisense oligonucleotide targeting heat shock protein 27 messenger RNA) was not more effective than the standard therapy of NP/G. While the formulation with necuparanib (heparin mimetic) was slightly superior to the placebo formulation, there was no significant improvement in OS and PFS, resulting in the same ORR as the NP/G standard therapy.

3. Conclusions

The effective and safe treatment of pancreatic cancer represents a major challenge for medical research. One of the strategies that research groups test is the combination of therapeutic agents and their effectiveness. Therapeutic agents currently being studied include ibrutinib, necuparanib, tarextumab, apatorsen, cisplatin, enzalutamide, and momelotinib. Only NP/G+necuparanib achieved a greater variation in overall survival than the NP/G regimen, while NP/G+cisplatin regimen is emerging as a candidate for an effective therapeutic strategy, although the phase 1b/2 study still has limitations. More studies should be conducted to corroborate the benefits of adding other drugs to the NP/G formulation.

Abbreviations and Acronyms

5-FU	Fluorouracil
AE	Adverse events
CNTs	concentrative nucleoside transporters

CTCAE	**Common Terminology Criteria for Adverse Events**
CR	**Complete response**
ENTs	**Equilibrative nucleoside transporters**
FOLFIRINOX	**Chemotherapy regimen containing fluorouracil, folinic acid, irinotecan, and oxaliplatin**
MMRI	**Molecular magnetic resonance imaging**
NP/G	**Nab-paclitaxel plus gemcitabine**
ORR	**Objective response rate**
OS	**Overall survival**
PDAC	**Pancreatic ductal adenocarcinoma**
PFS	**Progression-free survival**
TNBC	**Triple-negative breast cancer**
TNM	**Tumor/Node/Metastasis staging system from the American Joint Committee on Cancer**

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