

PERSPECTIVE

## Perspectives on chemotherapy-induced toxicities in pancreatic cancer

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**Abstract:** Despite breakthroughs in screening, identification, and therapy, pancreatic cancer (PC) remains a serious issue in cancer-related mortality. This comprehensive review investigates the long-term and latent effects of chemotherapy in PC, focusing on commonly used medicines such as gemcitabine, docetaxel, irinotecan, nab-paclitaxel, and others. Gemcitabine, a common PC medication, causes a variety of adverse effects, including myelosuppression and weariness. Combination therapy, such as docetaxel and irinotecan, enhance toxicity, resulting in problems such as neutropenia and gastrointestinal difficulties. Significantly, chemotherapy-related complications, such as thrombosis and cardiac difficulties connected to paclitaxel, present serious concerns. Erlotinib, gefitinib, vatalanib, and sunitinib studies show significant side effects. Despite ongoing challenges, determining the causes of the low objective response rate in gemcitabine-refractory patients remains challenging. The study emphasizes the importance of future advances in cancer etiology, arguing for large, straightforward studies examining combination chemotherapies to improve tolerance and minimize chemotherapy-induced sequelae. This overview serves as a thorough guide for physicians, researchers, and policymakers as they navigate the complex terrain of PC chemotherapy, providing significant insights to improve patient care.

**Keywords:** pancreatic cancer, chemoresistance, toxicities

Despite tremendous progress made in screening, detection, and treatment, pancreatic cancer (PC) is ranked in the fourth position among cancer-related deaths in United States [1]. It is projected that with improved treatment and early detection, the number of all cancer survivors will increase to over 20 million by 2026 [2]. According to GLOBOCAN 2016, almost 340,000 new cases of PC are diagnosed each year worldwide and PC is responsible for 331,000 deaths/year [3]. Chemotherapy is common treatment for all cancers that have extend from the primary tumor site. However, drug resistance to chemotherapy is a major impediment to patient survival and the leading cause of death in patients of the most advanced stage [4–6].

Over the last few decades, many anticancer therapies have been tested in the locally advanced and metastatic setting with reported mixed results. Many of these cancer survivors have long-term and latent effects from their treatment. Despite the improved efficacy and improved survival offered by modern treatments, the toxic side effects and long-term sequelae of chemotherapy remain a major source of concern for both patients and clinicians. In this perspective, we summarize the common long-term and latent treatment effects for PC. During the treatment of PC patients, doctors use various cytotoxic drugs and the side effects vary from one drug to another. Patients may experience various side effects during PC treatment detailed in [Table 1](#).

Gemcitabine monotherapy has been the standard of care for patients with PC since 1997 when it was shown to improve survival compared to 5-fluorouracil (5-FU) [7]. The common side effects of gemcitabine includes poor appetite, nausea, vomiting, diarrhea, myelosuppression, elevated liver enzymes, edema, rash, mouth sores, hair loss, sometimes change in liver or kidney function and extreme fatigue. The initial toxic effect of gemcitabine (1,000 mg/m<sup>2</sup> administration once weekly for 3 out of every four weeks) in PC has been demonstrated by Min *et al.* in 17 chemotherapy patients; they observed that the one-year survival rate was 18 % and is associated with both grade 3-4 leucopenia in 29% of patients [8].

A pilot study using the combination of docetaxel (65 mg/m<sup>2</sup>) and irinotecan (160 mg/m<sup>2</sup>) given on a 21-day cycle is associated with excess toxicity, mainly neutropenia, diarrhea, nausea

**Table 1** Chemotherapeutic drugs, their chemical essence, side effects, frequency and their significance for pancreatic cancer treatments

Chemo Drug	Chemical essence	Side Effects	Frequency	Significance	Reference
Gemcitabine	Nucleoside analog	Nausea, low blood counts, fatigue Liver abnormalities	Common Less Common	Standard chemotherapy for PC, used alone or in combination for advanced or metastatic cases.	[9]
FOLFIRINOX (5-FU, Leucovorin, Irinotecan, Oxaliplatin)	DNA synthesis inhibitor & Topoisomerase inhibitor	Diarrhea, neuropathy, neutropenia	Common	A combination therapy more aggressive than gemcitabine alone, used for metastatic pancreatic cancer in patients with good performance status.	[10]
Nab-Paclitaxel + Gemcitabine	Microtubule inhibitor	Neuropathy, fatigue, hair loss	Common	Combination used for the treatment of metastatic PC, improving survival rates over gemcitabine alone.	[11]
Erlotinib (Tarceva)	EGFR pathway	Rash, diarrhea Interstitial lung disease	Common Rare	Combination with gemcitabine for advanced PC, offering a modest survival benefit by targeting the EGFR pathway	[12]
Capecitabine	Thymidine synthesis inhibitor (Pyrimidine analog)	Hand-foot syndrome, diarrhea, nausea, vomiting Neutropenia, fatigue, abdominal pain Cardiotoxicity (chest pain, arrhythmias, etc.)	Common Common Less Common	An oral drug that metabolizes into 5-FU in the body, sometimes used in combination therapies	[13]

and vomiting in gemcitabine-refractory patients with advanced PC [14]. People receiving chemotherapy also are more likely to have low levels of white blood cells, red blood cells, and platelets leading to higher risk of anemia, infections, and hemorrhage [15]. In a phase I/II clinical trial on patients receiving 1,000 mg/m<sup>2</sup> of gemcitabine plus 125 mg/m<sup>2</sup> of nab-paclitaxel once a week for three weeks, showed sepsis and neutropenia toxicities. The most common grade 3-4 toxicities are fatigue, sensory neuropathy, and hematological toxicities including neutropenia, leukopenia, and thrombocytopenia [16].

Cancer can increase the risk of developing a blood clot known as thrombosis, and the chemotherapy may increase further risk of thrombosis. The cardiovascular complications such as venous thromboembolism, acute arterial events, and systemic capillary leak syndrome are common in cancer chemotherapy. A blood clot can cause chest pain and discomfort, redness, and swelling in a leg or arm, as well as shortness of breath. Paclitaxel is a microtubule-targeting anti-cancer agent that can result in cardiac problems. A study suggests that gemcitabine plus nab-paclitaxel is associated with congestive heart failure in advanced PC [17]. Paclitaxel, in combination with doxorubicin, also caused hypersensitivity neurotoxicity and palmar-plantar erythrodysesthesia in PC patients [18]. Peripheral neuropathy is observed as a side effect of nab-paclitaxel as well.

A combination treatment of raltitrexed and irinotecan in patients with gemcitabine-pretreated advanced PC showed adverse effects related to gastrointestinal, partial alopecia, and cholinergic syndrome [19]. Other studies also find similar results to neutropenia, fatigue, and diarrhea symptoms in gemcitabine-refractory metastatic PC treated with docetaxel 35 mg/m<sup>2</sup> followed by flavopiridol 80 mg/m<sup>2</sup> on days 1, 8, and 15 of a 28-day cycle [20]. Further, in metastatic PC patients, a gemcitabine containing regimen with pemetrexed 500 mg/m<sup>2</sup> as a 10-min infusion every three weeks showed hematological toxic effects including neutropenia, thrombocytopenia and anemia and non-hematological toxic effects such as diarrhea, nausea and stomatitis/pharyngitis [21]. The combination of 125 mg/m<sup>2</sup> of lipoplatin (liposomal cisplatin) and 1000 mg/m<sup>2</sup> of gemcitabine in advanced PC patients showed neutropenia as a primary symptom [22]. Gemcitabine + cisplatin combination in patients with advanced PC showed anemia or blood loss as the major adverse effects [23].

The erlotinib, an oral tyrosine kinase inhibitor (TKI) targeting the epidermal growth factor receptor (EGFR), is effective against PC [24, 25]. In gemcitabine resistance patients, the combination of capecitabine (1,000 mg/m<sup>2</sup>) and erlotinib (150 mg) shows significant toxicity of diarrhea and skin rashes [26]. In patients pretreated with gemcitabine-based chemotherapy, combination of docetaxel (75 mg/m<sup>2</sup>) and gefitinib (250 mg/day) administered every 3 weeks for a maximum of 6 cycles of treatment revealed neutropenia, fatigue, febrile, rash and diarrhea as common side effects [27]. The combination of gefitinib (250 mg/day orally) and docetaxel (75 mg/m<sup>2</sup>) for 21 days caused major febrile neutropenia, with fatigue, nausea, diarrhea and vomiting as common adverse effects [28]. Vatalanib is another oral poly-tyrosine kinase inhibitor targeting vascular endothelial growth factor (VEGF) receptors. Phase II trial of Vatalanib in PC patients who failed first-line gemcitabine-based therapy, showed significant symptoms of hypertension, fatigue, abdominal pain, and elevated alkaline phosphatase level [29]. The sunitinib, a multi-target TKI used to treat advanced PC patients with a dose of 50

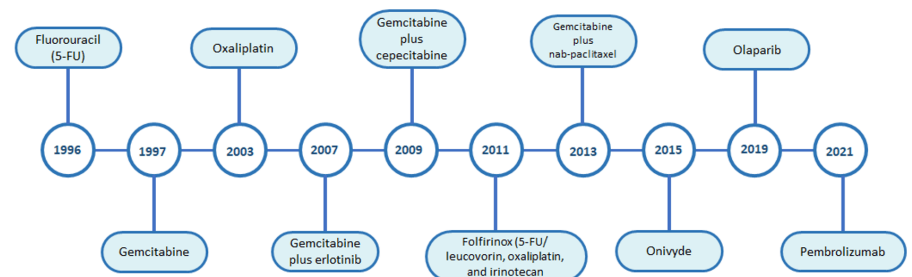
mg daily for 28 days. Sunitinib treatment in PC patients pretreated with gemcitabine-based chemotherapy showed severe fatigue, bleeding, nausea 4%, thrombosis / embolism, thrombotic thrombocytopenic purpura / renal failure, GI perforation and hematologic complication [30].

However, the exact reasons for the low objective response rate in PC patients who are refractory to gemcitabine are not fully known.

Gemcitabine refractory individuals, or those who do not respond to the chemotherapeutic medication gemcitabine, are commonly encountered in clinical practice, particularly in the treatment of PC. Gemcitabine has been a cornerstone of PC therapy, however resistance to this medicine is a substantial obstacle, typically resulting in restricted treatment alternatives and a poor prognosis for these patients. Gemcitabine resistance mechanisms are complicated and multidimensional; comprising changes in drug uptake and metabolism, apoptosis evasion, and activation of alternative survival pathways such as the Akt/mTOR pathway [31].

A subsequent study demonstrated that mTOR inhibitors were incapable of eliciting an objective response or disease stability, but rather created a negative feedback loop that resulted in disease progression and toxicity [32]. The Akt/mTOR pathway contributes to gemcitabine resistance in PC due to Annexin II, suggesting mTOR inhibitors could counteract this resistance [33]. Additionally, the PI3K-AKT-mTOR pathway and immunotherapies are under clinical investigation, reflecting the diverse nature of the disease [34]. Late-onset gemcitabine-induced severe pulmonary toxicity (GISPT) progresses rapidly, with death rates of 20%. Many studies reported that GISPT significantly impacts the early mortality of PC patients with pneumonia and veno-occlusive disease [35–37].

A recent large network meta-analysis demonstrated that FOLFIRINOX and Gemcitabine Pemetrexed regimens have a relatively higher incidence of toxicity in PC [38]. Certain chemodrugs used to treat PC have also been linked to adverse effects, including capecitabine, which can cause hand-foot syndrome, and oxaliplatin, which can cause peripheral neuropathy. The timeline depicted in Figure 1 illustrates the evolution of pancreatic cancer chemotherapeutic agents.



**Figure 1** The time line of advancement in chemotherapeutic agents in advanced pancreatic cancer

Despite multiple clinical trials and continuous efforts, PC remains one of the most challenging cancers to cure because of its aggressive characteristics and resistance to conventional chemotherapy. However, with advancements in early detection and treatment, cancer survivorship is expected to increase by 5 million globally over the next decade [39].

The presence of such resistance mechanisms necessitates the investigation of alternative therapeutic strategies, such as combination therapies that target the underlying resistance pathways, the use of newer chemotherapeutic agents, and the incorporation of targeted therapies and immunotherapies into treatment plans. Recent research and ongoing clinical trials are aimed at identifying predictive biomarkers that can help guide the selection of targeted medicines for particular patients, resulting in a more personalized approach to treatment [40]. This technique aims to enhance outcomes for gemcitabine-resistant individuals by personalizing therapy to the specific molecular profile of their tumor.

Although current drugs or other approaches to counteract chemotherapy-induced adverse effects are often incompletely effective, they frequently do not address potential longer-term sequelae or even induce other side effects, which only add to patient discomfort. In this context, advancements in cancer treatment require an increased understanding of cancer pathogenesis, mainly how cancer evolves. Further, preclinical and clinical studies with large simple trials using combination chemotherapies can be a promising approach to improve tolerance and reduce sequelae of cancer chemotherapy.

## Conflicts of Interest

The authors declare that they have no conflict of interest.

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