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NOVEL DRUG COMBINATIONS SUGGESTED FOR TREATING PANCREATIC CANCER

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Abstract

Pancreatic cancer (PC) is a type of gastrointestinal tumor with poor anticipation and high level of death rate, being a fatal disease in which the overall 5-year survival rate is less than 4%[1]. PC poorly responds to most chemotherapeutic agents and the main current systemic chemotherapy treatments for patients with advanced disease are the drug combinations FOLFIRINOX and gemcitabine plus nanoparticle albumin-bound (nab)-paclitaxel (Abraxane). Therefore, there is a profound world-wide unmet medical need for new drug combination treatments having significant positive impact on the survival and day-to-day functioning of PC patients. It is suggested herein that treatment of drug combinations of bevacizumab plus bortezomib or dacarbazine and decitabine and optionally interferon α can be beneficial for patients suffering from locally advanced and metastatic PC, subject to creating predictive models to determine possible drug resistance and receiving positive results in clinical trials.

Keywords: Pancreatic cancer, gastrointestinal tumor, chemotherapeutic agents, advanced and metastatic disease, drug combinations, drug resistance, clinical trials.

General Remak: The author has served for many years as a patent attorney and information specialist in a global pharmaceutical company, drafting patent applications and opinions relating to drugs for treating serious diseases such as cancer. As such, the information included herein, which is based on a literature search conducted on July 18, 2024, should be regarded as a general opinion on the drug combinations discussed in the present article.

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Introduction

Pancreatic cancer (PC) is a type of gastrointestinal tumor with poor anticipation and high level of death rate, being a fatal disease in which the overall 5-year survival rate is less than 4%. This figure has hardly improved over the past two decades. 80-85% of PC patients are typically diagnosed with advanced unresectable disease because of lack of or vague symptoms when the tumor is still localized.

Most of the pancreatic tumors have inception from the ductal epithelium of the pancreas consequently termed as pancreatic ductal adenocarcinoma (PDAC). Several types of PC are described as adenocarcinoma, a solid tumor that is the most common type of PC, accounting for more than 90% of diagnoses. This cancer occurs in the lining of the ducts in the pancreas and can develop from cells created by pancreatic enzymes. Another type is acinar cell carcinoma, which accounts for 1-2% of exocrine cancers. Squamous cell carcinoma is a rare nonendocrine cancer of the pancreas, formed in the pancreatic ducts, made of squamous cells, which are not seen in the pancreas. It has a bad prognosis because it is usually discovered after metastasis. Adeno-squamous carcinoma is an aggressive tumor with a poorer prognosis accounting for 1-4% of exocrine PCs. Compared with adenocarcinoma, adeno-squamous carcinoma is an aggressive tumor with a poorer prognosis. Colloid carcinoma accounts for 1-3% of exocrine PCs, which is originated from a type of an intraductal papillary mucinous neoplasm. Neuroendocrine PC, which accounts for 1-5% of PC cases, develops from cells in the endocrine gland of the pancreas, which secretes the hormones insulin and glucagon into the bloodstream to regulate blood sugar.

Patients with PC are often divided into several categories including locally advanced and metastatic PC but surgical resection is the only chance for cure. PC poorly responds to most chemotherapeutic agents and the main current systemic chemotherapy treatments for patients with advanced disease are the drug combinations FOLFIRINOX (5-fluorouracil, folinic acid [leucovorin], irinotecan, and oxaliplatin) and gemcitabine (an antimetabolite drug which was first prescribed for treating metastatic breast cancer) plus nab-paclitaxel. Said drug combinations of adjuvant chemotherapy improve the long-term outcomes in these patients.

Since PC poorly responds to most chemotherapeutic agents, there is a profound world-wide unmet medical need for new drug combination treatments having significant positive impact on the survival and day-to-day functioning of PC patients.

Clinical trials of drug combinations for treating PC

Several reviews have been published describing advances in oncological clinical trials of drug combinations[2,3,4]. As per the reports of the US National Library of Medicine (an official website of the United States government), the following are notable

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examples of drug combinations for treating PC. Clinical trial NCT01056601 tested a combination of panobinostat and bortezomib for treating PC progressing on gemcitabine therapy (Phase II, terminated). Clinical trial NCT06393166 tests a combination of Sequential AG and mFOLFOX combined with serplulimab injection and bevacizumab injection for treating advanced PC (Phase II, estimated completion date 31.12.2025). Clinical trial NCT00614653 tested a combination of bevacizumab, erlotinib and capecitabine for advanced PC (Phase I, completed in July 2016). Clinical trial NCT03351296 compares the effect of capecitabine + temozolomide (traditionally used for treating glioblastoma multiforme) and of 5-fluorouracil + streptozotocin given with a new schedule (5-fluorouracil + streptozotocin), two of the most used chemotherapy regimens in the treatment of well differentiated pancreatic neuroendocrine tumors alone or in combination with bevacizumab on progression-free survival and compare the chemotherapy regimens alone or with bevacizumab (two by two design) on the same criteria (Phase II, estimated completion in December 2028). Clinical trial NCT00112528 tested a combination of bevacizumab, gemcitabine, and oxaliplatin in treating patients with metastatic PC (Phase II, completed in November 2010). Clinical trial NCT02340117 combined tumor-targeting *TP53* gene therapy with gemcitabine/nab-paclitaxel as a second-line treatment for metastatic PC (Phase II, completed on 31.12.2022). Clinical trial NCT02432963 studied p53MVA vaccine in combination with pembrolizumab for treating uncontrolled solid tumors with p53 over-expressions or mutations (Phase I, completed in May 2017). Clinical trial NCT02433626 studied COTI-2 (a novel anti-cancer thiosemicarbazone agent having low toxicity) as a monotherapy or combination therapy with cisplatin for the treatment of malignancies (Phase I, completed in June 2020). Clinical trial NCT00497224 tested erlotinib in addition to gemcitabine in patients with metastatic or locally advanced, unresectable PC who have received up to one line of gemcitabine-based chemotherapy, which significantly improved overall survival compared to gemcitabine alone in advanced PC (median overall survival 6.24 vs 5.91 months respectively). However, the combined therapy has not become standard of care due to the modest absolute benefit. Clinical trial NCT06241353 investigates the role of statins in treating PC by assessing the safety and therapeutic impact of combining chemotherapy with statins in patients with advanced PC (Phase II, estimated to be concluded in February 2027). There are several clinical studies using interferon α together with chemotherapeutic agents and other means of therapy such as radiation for treating PC, e.g., clinical trial NCT00082862 for treating patients with inoperable or metastatic PC with combination of gemcitabine, cisplatin, metronomic low-dose interferon α and fever-range whole-body hyperthermia (Phase II which is estimated to be concluded in February 2027). Clinical trial NCT05360264 is designed to assess the therapeutic efficacy of decitabine repurposing against advanced, refractory PDAC with molecular transcriptional signatures indicating dependency on the KRAS oncogene (Phase II, which is estimated to be concluded in February 2025). Clinical trial NCT0645448, is designed to assess the therapeutic efficacy of adebrelimab in combination with decitabine, albumin-bound paclitaxel and gemcitabine for the first-line treatment of metastatic PC (Phase Ib/II, which is estimated to be concluded in February 2025).

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Discussion

According to B. He et al[5], drug combinations may have antagonistic, additive or synergistic effect in cases where the combined effect is less than, equal to or greater

than the sum of the individual drugs. The authors describe the example of using gemcitabine + nab-paclitaxel for treating PC. The authors argue that while synergistic drug combination is useful, antagonistic drug combination may also be beneficial by reducing the evolution of drug resistance because it cures the disease faster, thereby limiting the time window available for drug resistant mutations to accumulate and increasing the selective advantage of drug-resistant mutants.

While considering treatment with a drug combination, drug resistance should be considered. According to C. Munck et al.[6], drug resistance can arise during chemotherapeutic treatment and in particular during long-term treatment. Although drug combinations may reduce the evolution of drug resistance, predictive models are needed to design resistance-limiting therapeutic regimens.

Synergistic or antagonistic interactions among the components of the drug combination can be discovered in clinical studies while the drugs' mechanisms of action and pharmacokinetics may be evaluated in pre-clinical studies.

According to H.F Hu et al., oncogenic mutations in the KRAS gene, which is mutated in about 93% of PCs, and the loss of function mutations in the tumor suppressors TP-53, CDNK2A, DPC4/SMAD4 and BRCA2 are frequently observed in PDAC[7]. KRAS is a challenging therapeutic target because the data concerning it is constantly being updated by a growing number of studies although KRAS inhibitors, such as sotorasib, targeting the specific mutation G12C in the treatment of non-small-cell lung cancer, and adagrasib for treating same, show positive results in clinical trials.

KRAS mutation and alteration in CDNK2A are early events in pancreatic tumorigenesis. Currently there are no cancer treatments approved specifically for patients with a CDKN2A mutation, nor written guidelines for treating cancer specifically for people with a CDKN2A mutation. Patients with a CDKN2A mutation who are diagnosed with cancer may benefit from biomarker testing and may qualify for clinical trials looking for more effective treatments for cancer. The KRAS mutation alone is insufficient to drive carcinogenesis and changes in other gene expressions cooperate to drive the formation of the final invasive PDAC.

TP53 is a genome guardian governing the cell response which results in cell cycle arrest, DNA damage repair, apoptosis and senescence. The mutational status of TP53 has an impact on the response to DNA damage and somatic mutations in the gene leading to carcinogenesis. Deficiency of the nuclear transcription factor with pro-apoptotic function P53 integrates with telomere dysfunction and cause acceleration of carcinogenesis.

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According to D. P Lane et al., treating mice with the proteasome inhibitor bortezomib stabilized p53 in stem/progenitor cells of the intestine and stomach, in other proliferating tissues, and in intestinal tumors[8]. The research group reported that robust basal p53 mRNA levels were observed in the same compartments where p53 was stabilized and concluded that although bortezomib is less active in p53-defective tumors, it's use can be extended to p53-proficient solid tumors.

V. Heinemann et al., describe two treatment strategies in advanced PC, a reference sequence of gemcitabine/erlotinib followed by second-line capecitabine compared with a reverse experimental sequence of capecitabine/erlotinib followed by gemcitabine that show significant improvement in combination of erlotinib with gemcitabine with a survival advantage observed in patients with tumors expressing wild-type KRAS when erlotinib was prescribed with gemcitabine/capecitabine, median survival rates of 7.9 months and 5.7 months respectively for patients with wild-type KRAS and mutated KRAS[9].

Referring to the clinical trials of treating patients with a combination of panobinostat and bortezomib in PC progressing gemcitabine therapy, it is mentioned that cancer results from multiple mutations cause cells to grow uncontrolled and therefore it is necessary to inhibit several oncogenic targets to control cancer cell growth. Studies have shown that panobinostat causes a wide range effect on endothelial cells that lead to inhibition of tumor angiogenesis, which is a fundamental step in the transition of tumors from a dormant state to a malignant one. Bortezomib triggers cell death in PC cells although the mechanism is not well defined but the drug's effect has been determined to be cytostatic.

R.K Ramanathan et al., describe a phase II clinical trial of dacarbazine (a triazole carboxamide molecule) in advanced pancreatic islet cell carcinoma (pancreatic endocrine tumor or pancreatic neuroendocrine tumor). According to the authors, dacarbazine is a non-classic synthetic alkylating agent having single agent activity in metastatic malignant melanoma, Hodgkin's disease, sarcomas, childhood neuroblastomas and primary brain tumors. The results show that dacarbazine has activity in advanced previously untreated pancreatic islet cell tumors with median survival overall of 19.3 months. However, a total of 16 patients out of 54 (30%) had grade 3 (severe) and grade 4 (potentially life-threatening) toxicities[10]. According to the European Chemicals Agency, this substance may cause cancer and genetic defects and in addition it may cause serious respiratory, eye and skin irritations and it is harmful if inhaled or swallowed.

It is widely recognized that extremely toxic drugs are rarely approved for use. Analyzing a drug’s safety is complicated because of the balance between its beneficial therapeutic effects and whether or not it has any severe or life-threatening side effects. Regulators must decide whether the drug’s benefits outweigh its potential harms. However, a third-line cancer drug with potential severe side effects might be considered reasonably safe, due to the severity of the condition being treated.

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Eriksson et al. reported that 22 patients with advanced malignant endocrine pancreatic tumors were treated with human leucocyte interferon and objective responses were more than 50% reduction in tumor markers or size and median response duration of 8.5 months while all responders improved clinically and adverse effects seemed more tolerable than those of cytotoxic treatment[11].

According to the clinical data described above, it is suggested herein that treatment of drug combinations of bevacizumab plus bortezomib or dacarbazine and decitabine and optionally interferon α can be beneficial for patients suffering from locally advanced and metastatic PC, subject to creating predictive models to design resistance-limiting therapeutic regimens and receiving positive results in clinical trials that include toxicity studies.

Legal status

Bortezomib and decitabine are included in the current FDA's prescription list of off-patent, off-exclusivity drugs without an approved generic. Dacarbazine received FDA approval in May 1975 under the trade name DTIC-Dome and it is available as a lower-cost generic. There are currently at least four FDA-approved biosimilars to bevacizumab (Avastin). They include Mvasi (bevacizumab-awwb), Zirabev (bevacizumab-bvzr), Alymsys (bevacizumab-maly) and Vegzelma (bevacizumab-adcd).

Conclusion

PC is defined as a serious condition that if left untreated will progress from a more serious to life-threatening condition in advanced unresectable disease patient cases. Said drug combinations for treating PC, described above, may have a positive impact on the survival and day-to-day functioning of the patients. Therefore, clinical trials of the novel suggested drug combinations, aimed to treat serious conditions, fill an unmet medical need and can serve as suitable candidates for fast-track clinical trials, which are processes designed to facilitate the development, and expedite the review of drugs for treating serious conditions that fill such unmet medical needs. The purpose is to get novel effective drug combinations to the patients as early as possible.

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