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LETTER TO THE EDITOR

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LETTER TO THE EDITOR

Future therapies for pancreatic carcinoma: Insights into cancer precision medicine

Qiu-Yu Jiang, Zhi-Xue Chen, Si Zhang, Ru-Yi Xue

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Abstract

Pancreatic carcinoma (PC) has one of the highest rates of cancer-related death worldwide. Except for surgery, adjuvant chemotherapy, chemoradiotherapy, and immunotherapy have shown various efficacies depending on the stage of the patient. We read the review "Current and emerging therapeutic strategies in pancreatic cancer: Challenges and opportunities" and offer some opinions that may improve its precision and completeness. This review presents a map of appropriate therapies for PC at different stages. Based on the clinical trial outcomes mentioned in the review, we evaluated the potential therapeutic options for PC and helped explain the contradictory efficacy between different programmed cell death protein 1/programmed cell death ligand 1 clinical trials, which may have resulted from the unique features of PC. Although R0 resection and adjuvant chemotherapy are still the gold standards for PC, new modalities, with or without clinical validation, are needed to establish more specific and precise treatments for PC.

Key Words: Pancreatic carcinoma; Immunotherapy; Chemotherapy; Radiochemotherapy; Future therapies

Core Tip: For the treatment of pancreatic carcinoma (PC), although surgery with adjuvant chemotherapy or chemoradiotherapy remains the gold standard for most patients, attention needs to be given to immunotherapy and other research hotspots. In addition to programmed cell death protein 1/programmed cell death ligand 1, we suggest that immunotherapies such as agonistic CD40, adoptive T cell therapy, myeloid-targeted therapies, stroma-targeted therapies, multiple immunomodulatory agents, and other treatments such as small-molecule inhibitors, antibodies, or viruses targeting tumors, as well as gene editing techniques, may help improve the prognosis of patients with PC in the future.

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TO THE EDITOR

We read with interest the review "Current and emerging therapeutic strategies in pancreatic cancer: Challenges and opportunities" by Manrai *et al*[1], who summarized the current and emerging therapeutic strategies in pancreatic cancer (PC). We agree with the main thrust of this review and want to share some ideas after a careful review and further analysis of this article.

First, we consider this topic to be of practical significance. PC is a rare cancer (3.2% in the United States in 2020[2]), but with increasing incidence and mortality (5-year overall survival: 9% in the United States[2]), it remains a burden worldwide without promising effective therapies. In this review, the authors systematically summarized the mainstream clinical trial outcomes and focused on the challenges and available treatment modalities for PC at different stages, especially the standard management of resectable, borderline resectable, locally advanced, and advanced metastatic PC. The standard management for resectable or borderline resectable PC is surgery followed by adjuvant chemotherapy. The efficacy of adjuvant or neoadjuvant chemotherapy and chemoradiotherapy has been assessed in several clinical trials. The standard treatment for locally advanced and advanced metastatic PC is gemcitabine-based chemotherapy. In addition, newer potential modalities such as immunotherapy, targeted therapy, macrophage-targeted therapy, and cancer vaccines were also mentioned, providing researchers with guidelines for present clinical applications and future research work.

Second, the efficacy of the targeted agent erlotinib in combination with gemcitabine may depend on the different stages of PC, as confirmed by various clinical trials. In contrast to the efficacy shown in patients with metastatic PC, we found that two large clinical trials that focused on different stages of PC showed little benefit. The phase III LAP07 trial in 2016 investigated the clinical value of erlotinib combined with gemcitabine in patients with locally advanced PC. Unfortunately, the median overall survival of patients who received gemcitabine alone was 13.6 mo [95% confidence interval (CI): 12.3–15.3 mo] compared with 11.9 mo (95%CI: 10.4–13.5 mo) for patients receiving gemcitabine plus erlotinib[3]. The multicenter randomized phase III CONKO-005 Trial in 2017[4] assessed this combination therapy in patients with resectable PC after R0 resection and showed median disease-free survival of 11.4 mo *vs* 11.4 mo (gemcitabine alone) and median overall survival of 24.5 mo *vs* 26.5 mo. To date, such targeted agents combined with conventional chemotherapy may not show much of an advantage. We expect to see more advances in the future.

Thirdly, in the section "Immunotherapy for pancreatic cancer," the authors stated that popular programmed cell death protein 1/programmed cell death ligand 1 (PD-1/PD-L1) suppressor pembrolizumab had limited performance in the phase II KEYNOTE-158 study, due to the rare metastatic microsatellite instability in PC. This type of poor reactivity has been explained by several unique factors in PC: The well-recognized suppressive elements in the tumor microenvironment; the functional and structural barrier imposed by stromal components; T-cell exhaustion; possible choice of the wrong immune targets; and microbial factors, including gut dysbiosis and the unexpected presence of tumor microbes[5]. We agree with this, but we want to add that the clinical feasibility of PD-1 inhibitors deserves to be recognized. Recently, several clinical trials have examined the efficacy of conventional chemotherapy in combination with PD-1 inhibitors and other antagonists that mobilize T-cell activation and have shown mild but promising success. The phase IIa COMBAT trial in 2020 utilized the CXC chemokine receptor 4 antagonist BL-8040 (motixafortide), which promoted T-cell tumor infiltration, combined with pembrolizumab and chemotherapy in metastatic pancreatic adenocarcinoma, showing that BL-8040 may increase the benefit of chemotherapy. It reveals an overall response rate of 32%, disease control rate of 77%, and median duration of response of 7.8 mo[6]. Another phase I ARC-8 trial in 2021 also preliminarily validated the feasibility of combining chemotherapy with the PD-1 inhibitor zimberelimab and AB680, which is an inhibitor of CD73, to reduce adenosine generation and thus proliferating T cells. Eleven of the 13 patients who received treatment for at least 16 wk experienced

tumor shrinkage or stabilization[7,8]. Although the outcomes were not significant, they were encouraging, and future larger controlled studies are needed, and we are hopeful of good results. We believe that the abovementioned factors will be discussed in the future.

Importantly, except for the newer modalities mentioned in the review, we found that more therapies should be included. According to previous studies, other opportunities for PC immunotherapy, such as agonistic CD40, adoptive T cell therapy, myeloid-targeted therapies, stroma-targeted therapies, and multiple immunomodulatory agents are worthy of attention, and their efficacy in various PC stages has been proven by numerous clinical trials[9].

In conclusion, this review provides a valuable clinical reference for the management of PC, helping young clinicians to learn of appropriate clinical strategies for PC. It sheds light on different strategies for dealing with PC at different stages. In addition, it summarizes both the gold standard treatments and new therapeutic strategies such as immunotherapy and targeted therapy, which can guide clinicians and researchers to find a more promising combined treatment for PC. Recently, in different types of cancer, small molecule inhibitors, antibodies, or viruses targeting tumors, as well as gene editing techniques like CRISPR-Cas9 have shown antitumor potential, based on abundant research. We should always keep in mind that although early diagnosis and R0 resection are the first and best choice for PC patients, adequate basic research is still needed aimed at new targets or mechanisms that may provide patients with more specific and precise medical care to improve their prognosis.

FOOTNOTES

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