Name of Journal: World Journal of Gastroenterology

Manuscript NO: 72934

Manuscript Type: LETTER TO THE EDITOR

Future therapies for pancreatic carcinoma: letter to “Current and emerging therapeutic strategies in pancreatic cancer: Challenges and opportunities”

Qiu-yu Jiang et al. Future therapies for pancreatic carcinoma

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Abstract
Pancreatic carcinoma (PC) is one of the most severe types 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 this review “Current and emerging therapeutic strategies in pancreatic cancer: Challenges and opportunities” and added some opinions that help to improve its precision and completeness. This review presents a map of appropriate therapies for pancreatic carcinoma at different stages. Based on the clinical trial outcomes mentioned in the review and we found, we evaluated the potential therapeutic options for PC and helped explain the contradictory efficacy between different PD-1/PD-L1 clinical trials, which may result from unique factors of PC. Although R0 resection and adjuvant chemotherapy are still the gold standards for PC patients, other new modalities with or without clinical validation still need our efforts to help determine more specific and precise treatments for PC patients.

Key Words: Pancreatic carcinoma; Immunotherapy; Chemotherapy; Radiochemotherapy.


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 aroused to the immunotherapy and other hotspots. In addition to PD-1/PD-L1, we thought that immunotherapies such as agonistic CD40, adoptive T cell therapy, myeloid-targeted therapies, stroma-targeted therapies, multiple immune-modulatory 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.

TO THE EDITOR

We read with great interest the review “Current and emerging therapeutic strategies in pancreatic cancer: Challenges and opportunities” by Manrai et al.\textsuperscript{[1]}, who summarized the current and emerging therapeutic strategies in pancreatic cancer. We agree with the main idea 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. Pancreatic carcinoma is a rare cancer (3.2\% in the USA in 2020\textsuperscript{[2]}), but with increasing incidence and mortality (5-year OS: 9\% in the USA\textsuperscript{[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 modalities of pancreatic carcinoma (PC) at different stages, especially the standard management of resectable, borderline resectable, locally advanced, and advanced metastatic pancreatic cancer. 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 (GEM). In addition, newer potential modalities such as immunotherapy, targeted therapy, macrophage-targeted therapy, and cancer vaccines were also mentioned clearly, providing young medical scholars with an ensuring guideline 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 good efficacy shown in metastatic PC patients, as mentioned in the review, we found that two large clinical trials focusing on different stages of pancreatic cancer to date have shown little benefit. The phase III LAP07 trial in 2016 was pitched at
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% CI, 12.3-15.3 mo) whereas 11.9 mo (95% CI, 10.4-13.5 mo) for patients receiving gemcitabine plus erlotinib\textsuperscript{[3]}. Another multicenter randomized phase III CONKO-005 Trial in 2017\textsuperscript{[4]} assessed this combination therapy in patients with resectable PC after R0 resection and also showed the 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 drugs 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 introduced that popular 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 pancreatic cancer: the well-recognized suppressive elements in the tumor microenvironment, the functional and structural barrier imposed by stromal components, T-cell exhaustion, the choice of perhaps the wrong immune targets, and microbial factors, including gut dysbiosis and the unexpected presence of tumor microbes\textsuperscript{[5]}. We agree with this, but we want to add that the clinical feasibility of PD-1 inhibitors deserves to be observed. Recently, several clinical trials have examined the efficacy of conventional chemotherapy in combination with PD1 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 PDAC, showing that BL-8040 may expand the benefit of chemotherapy. It reveals an overall response rate (ORR) of 32%, disease control rate (DCR) of 77%, and median duration of response of 7.8 mo\textsuperscript{[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, a bit
encouraged, and future larger controlled studies are needed, and we could expect the
good fate of the hottest immune checkpoint inhibitor with some hope. 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 to be included. According to previous studies, other hotspot
opportunities for PC immunotherapy, such as agonistic CD40, adoptive T cell therapy,
myeloid-targeted therapies, stroma-targeted therapies, and multiple immune-
modulatory agents also worth our attentions, whose efficacy in various PC stages have
been proven by numerous clinical trials\(^9\).

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