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Editorial Board Member of *World Journal of Gastroenterology*, Dmitry S Bordin, MD, PhD, Chief Doctor, Professor, Department of Pancreatic, Biliary and Upper GI Tract Diseases, A.S. Loginov Moscow Clinical Scientific Center, Moscow 111123, Russia. dmitrybordin@gmail.com

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LETTER TO THE EDITOR

Discussion on gemcitabine combined with targeted drugs in the treatment of pancreatic cancer

Jun-Hao Huang, Wei Guo, Zhe Liu

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Jun-Hao Huang, Wei Guo, Zhe Liu, Department of Pancreatic-Biliary Surgery, The First Hospital of China Medical University, Shenyang 110001, Liaoning Province, China

Corresponding author: Zhe Liu, MD, Doctor, Professor, Surgeon, Department of Pancreatic-Biliary Surgery, The First Hospital of China Medical University, No. 155 Nanjing North Street, Heping District, Shenyang 110001, Liaoning Province, China. liuzhe4321@126.com

Abstract

Pancreatic cancer is a malignant tumor with poor prognosis. The treatment of pancreatic cancer depends on the tumor stage and type, and includes local treatment (surgery, radiotherapy and ablation intervention) and systemic therapy (chemotherapy, targeted therapy and immunotherapy). We read with great interest the review "Effective combinations of anti-cancer and targeted drugs for pancreatic cancer treatment" published on *World J Gastroenterol* and intended to share some of our perspectives in pancreatic cancer treatment. This review presents the therapeutic effects of the combination of gemcitabine and targeted drugs, which gives us a deeper insight into the combination treatments for pancreatic cancer.

Key Words: Pancreatic cancer; Chemotherapy; Targeted therapy; Gemcitabine; Drug; Combination

Core Tip: In terms of the choice of chemotherapy regimen for pancreatic cancer, multi-drug chemotherapy is often applied in clinical practice. In general, the combination of chemotherapy and targeted therapy have better efficacy, but whether the combination of the two schemes is more effective than chemotherapy alone requires further investigations.

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TO THE EDITOR

We have read with great interest the review "Effective combinations of anti-cancer and targeted drugs for pancreatic cancer treatment" published on *World J Gastroenterol*[1]. As is known, gemcitabine alone had limited efficacy in the treatment of pancreatic cancer. This review reported that gemcitabine in combination with targeted agents, like the combination of gemcitabine and Chk1 inhibitor, gemcitabine and KRAS antibody/MEK inhibitor, gemcitabine and autophagy inhibitor, had better efficacy. In addition, the combination of targeted drugs also resulted in better clinical outcome, such as ERK and autophagy inhibitors; ERK, Chk1, and autophagy inhibitors; 2-deoxyglucose and MEK inhibitors; replication stress response and autophagy inhibitors; and immune checkpoint and autophagy inhibitors. It is interesting to note that some natural products, such as cucurbitacin B and glaucarubinone, also had better therapeutic effects in pancreatic cancer when combined with other drugs or with other natural products[1]. We agree with the authors that the combination could improve the therapeutic efficacy in patients with pancreatic cancer. Based on this review and our clinical experience we here share some of perspectives about pancreatic cancer treatment.

According to the National Comprehensive Cancer Network guidelines, there are many methods of chemotherapy used for treating pancreatic cancer, including multi-drug chemotherapy. The current standard first-line treatment regimen for metastatic pancreatic cancer includes gemcitabine and albumin-bound paclitaxel or modified FOLFIRINOX (leucovorin, fluorouracil, irinotecan, oxaliplatin)[2, 3]. A study of 861 untreated patients with metastatic pancreatic cancer has reported a better efficacy of gemcitabine and albumin-bound paclitaxel compared with gemcitabine [median survival, 8.5 *vs* 6.7 mo; hazard ratio = 0.72, 95% confidence interval (CI): 0.620-0.83; $P < 0.001$)[4]. In the current clinical practice, gemcitabine is rarely used alone. This review pointed out that gemcitabine was used for chemotherapy combined with various targeted drugs, but did not mention whether gemcitabine and albumin-bound paclitaxel combined with targeted drugs have better effects, which is important in the treatment of this cancer and needs to be identified. Targeted drugs combined with gemcitabine may have variable efficacy for different stages of pancreatic cancer. The review reported that gemcitabine combined with some targeted drugs yielded better clinical outcome, however, in our opinion, the combination is not always as effective as we expect, which may be worth discussion. The phase III LAP07 trial in 2016 investigated the clinical value of erlotinib combined with gemcitabine in patients with locally advanced pancreatic cancer. The median overall survival of the patients treated with gemcitabine alone was 13.6 mo (95%CI: 12.3-15.3 mo), while the patients receiving gemcitabine combined with erlotinib had a median overall survival of 11.9 mo (95%CI: 10.4-13.5 mo). The combination *vs* gemcitabine alone, despite good adherence, failed to improve survival and was associated with increased grade 3 hematologic, digestive, and skin toxicity[5]. CONKO-006 was a randomized double-blinded phase IIb study designed to evaluate the efficacy of the combination of gemcitabine and sorafenib compared with gemcitabine and placebo in patients with pancreatic adenocarcinoma with postsurgical R1 residual status. The results indicated that there were no differences in recurrence-free survival nor overall survival between the two groups[6]. The exact mechanism by which the combination of drugs could be less effective than gemcitabine alone is difficult to explain and may be related to the greater toxicity of combination drugs. An open-label, multicenter, randomized phase II trial evaluated gemcitabine plus afatinib *vs* gemcitabine alone for metastatic pancreatic cancer. Median overall survival was 7.3 mo with gemcitabine plus afatinib *vs* 7.4 mo with gemcitabine alone. Adverse events like diarrhea and rash were more frequent with gemcitabine plus afatinib[7]. In brief, these studies remind us that different combinations of chemotherapeutic drugs and targeted drugs may have different effects for various stages of pancreatic cancer. In conclusion, this review has led us to focus on new options of pancreatic cancer treatment, which is significant in guiding the clinical pancreatic cancer treatment and pointing out the direction for future research.

FOOTNOTES

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Country/Territory of origin: China

ORCID number: Jun-Hao Huang 0000-0001-6501-599X; Wei Guo 0000-0003-0375-0950; Zhe Liu 0000-0003-2950-3966.

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