Electrochemotherapy for Pancreatic Cancer: An Emerging Treatment Modality?

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Electrochemotherapy is defined as using electroporation to improve the delivery of chemotherapy drugs into cells.¹ Since the 1990s, electrochemotherapy of cutaneous melanoma with bleomycin and cisplatin has achieved an objective response rate of 85%.² However, its application to intra-abdominal malignancy has only been tested in the liver.³ Electrochemotherapy in pancreatic adenocarcinoma has not been well established.⁴ Because of delayed diagnosis and early recurrence, pancreatic adenocarcinoma has been generally considered as a systemic disease.⁵ Local treatments alone, such as aggressive surgical resection or radiation therapy, can only help some patients with localized pancreatic adenocarcinoma. Potent and effective chemotherapies such as fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) or gemcitabine/nab-paclitaxel have resulted in improved systemic control and changed the treatment paradigm.⁶ With improved systemic control, there has been a cascade of publications on aggressive local control of advanced pancreatic adenocarcinoma after chemotherapy.⁷

In the article that accompanies this editorial,⁸ Martin et al. published their preliminary experience on a novel electrochemotherapy approach using irreversible electroporation (IRE) and modern chemotherapy regimens, including gemcitabine/nab-paclitaxel or FOLFIRINOX. The group led by Martin et al. has pioneered the application of IRE in the treatment of advanced pancreatic adenocarcinoma.⁹ Over the last decade, Martin's group and others have shown the feasibility and effectiveness of IRE

for patients with locally advanced pancreatic cancer. A novel electrochemotherapy approach using IRE and active chemotherapy agents can improve drug delivery to the complex tumor microenvironment of pancreatic cancer. Using the orthotopic mouse model, Martin et al. showed this electrochemotherapy approach had a synergistic treatment effect via the apoptosis pathway and anti-proliferation mechanism. What is more intriguing than the results from the mouse model is the safety and efficacy outcome from five patients with stage three pancreatic cancer treated with this electrochemotherapy approach. They observed no toxicity or disease progression at a median follow-up of 81 days after the surgery.

Martin's group is to be commended for this well-designed comprehensive preclinical study. This novel electrochemotherapy approach has great potential in helping patients with advanced pancreatic cancer. Like many other exciting studies, more information is needed to fill in certain knowledge gaps. First, data from prospective studies on electrochemotherapy are urgently needed to help patients with pancreatic cancer. It is exciting to know that Martin's group has started a prospective dose-escalating safety and tolerability study of chemotherapy and IRE in the treatment of advanced pancreatic adenocarcinoma (NCT03484299). All patients undergoing IRE by experienced surgeons will receive chemotherapy with FOLFIRINOX or gemcitabine. This prospective study will lay the foundation for future randomized efficacy studies. Second, many high-volume centers of pancreatic surgery don't have the proper setup or adequate experience to perform IRE. Being able to educate other pancreas surgeons to master IRE will be the key to conducting multi-center prospective studies of electrochemotherapy in the future. Finally, the tumor microenvironment in patients with pancreatic cancer is complex. Whether the electrochemotherapy approach using IRE and FOLFIRINOX

can improve the tumor antigen presentation or affect tumor immunogenicity is unknown. With the success of immune checkpoint inhibitors in many other solid tumors, the potential of combining electrochemotherapy and immune checkpoint inhibitors remains to be defined.

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