CANCER DIAGNOSIS & PROGNOSIS *5*: 280-284 (2025)
doi: 10.21873/cdp.10440

Perspective on an Innovative Curative Strategy for Peritoneal Metastasis Involving Peritonectomy, Hyperthermic Intraperitoneal Chemotherapy, and Adjuvant Chemotherapy Identified as Effective in the Histoculture Drug Response Assay (HDRA)

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Abstract

Background/Aim: Peritoneal carcinomatosis is the end stage for patients with gastrointestinal cancer, with survival ranging between 2 and 9 months. Pancreatic acinar cell carcinoma (PACC) is rare and can result in peritoneal metastases. The efficacy of chemotherapy for patients with PACC is unknown, and a systemic treatment strategy has not been established. The aim of the present perspective is to discuss a potential curative strategy combining surgery, heated intraperitoneal chemotherapy (HIPEC), and the histoculture drug response assay (HDRA) to identify effective adjuvant chemotherapy for PACC with peritoneal metastases, based on a published case report.

Case Report: A 31-year-old man with a 20 cm epigastric mass, diagnosed as PACC, had curative-intent resection of a tumor on the distal stomach and pancreas tail. The patient recurred after four courses of adjuvant oral S-1 treatment. Laparotomy demonstrated peritoneal metastases with a peritoneal cancer index of 18. Ascites or other cancer cells in the peritoneal wash were not found. Peritonectomy, combined with HIPEC with gemcitabine and docetaxel, was performed intraoperatively. Postoperative 3-dimensional histoculture of fragments of the resected tumor with drug response testing with the histoculture drug response assay (HDRA) showed gemcitabine had the highest tumor

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Received February 25, 2025 | Revised March 13, 2025 | Accepted March 14, 2025

inhibitory rate (70%) among six drugs tested. Based on the HDRA results, the patient was treated with adjuvant systemic gemcitabine chemotherapy. The patient did not have a recurrence within 18 months after surgery.
Conclusion: The present innovative treatment of PACC with peritoneal metastases used laparotomy to determine the extent of peritoneal metastases, peritonectomy to attempt to completely remove the tumor, HIPEC for intraoperative hyperthermic-chemotherapy, and the HDRA to determine the most effective drug for adjuvant chemotherapy. These procedures can be individualized for each patient's cancer, and the HDRA is most critical for individualization.

Keywords: Peritoneal metastasis, peritonectomy, hyperthermic intraperitoneal chemotherapy, HIPEC, histoculture drug response assay, HDRA, adjuvant chemotherapy, gemcitabine, pancreatic acinar cell carcinoma, cure.

Introduction

Peritoneal metastasis is the end stage for patients with gastrointestinal cancer, with no known effective therapy.

The exocrine pancreas comprises more acinar cells than ductal cells but most pancreatic cancers are ductal, and pancreatic acinar-cell carcinoma (PACC) is rare, approximately 1-2% of all pancreatic cancers (1-6). PACC is usually high grade, occurring in the head of the pancreas but can occur elsewhere in the pancreas (7-9). There is no first-line therapy for PACC and it relies on surgical resection with negative margins (6, 10). PACC is usually 10-11 cm when diagnosed (11-13). PACC is highly malignant with 50% of the patients presenting with metastasis when they are diagnosed with PACC. However, peritoneal metastasis is rare for PACC patients at the time of diagnosis of pancreatic cancer (14).

In PACC, there are no systematic studies to test the efficacy of chemotherapy, therefore effective therapy is unknown (3, 15-18). Heated intraperitoneal chemotherapy (HIPEC) is used intraoperatively for PACC peritoneal metastasis, but benefits have not been shown.

Recently, the Japanese group headed by Dr. Yutaka Yonemura has published a case report on a patient with PACC who had their extensive peritoneal metastasis resected and received intraoperative HIPEC with gemcitabine and docetaxel (1). The patient also received adjuvant gemcitabine that was identified as effective by the histoculture drug response assay (HDRA) (19-23) using a resected tissue sample of the peritoneal metastasis placed in 3-dimensional (3-D) histoculture (1).

The purpose of the present perspective is to discuss an innovative potential curative strategy for peritoneal metastasis with surgery, HIPEC, HDRA, and adjuvant chemotherapy, based on the case report (1).

Case Report

A 31-year-old man presented with a 20 cm epigastric mass on the pancreas tail, which adhered to the posterior wall of the stomach.

An *en bloc* resection of the distal stomach and distal pancreas was initially performed.

The resected tumor was diagnosed as PACC by histology. Adjuvant oral S-1 therapy was administered for four cycles. The cancer recurred approximately three years later with peritoneal dissemination. 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) were then administered without efficacy for three courses. White-colored round nodules ranging from 2 mm to 20 mm occurred on the peritoneal surface with a peritoneal cancer index (PCI) of 18 that was visualized by laparotomy. A peritoneal wash did not produce ascites or other cancer cells.

A right sub-diaphragmatic peritonectomy and a pelvic peritonectomy to remove the peritoneum on both sides of the para-colic gutter was performed. Additionally, three sections of the small-bowel mesentery with peritoneal metastases were also removed. The peritoneal cavity was then washed with 10 liters of saline. HIPEC was performed with one gram of gemcitabine and 60 mg docetaxel.

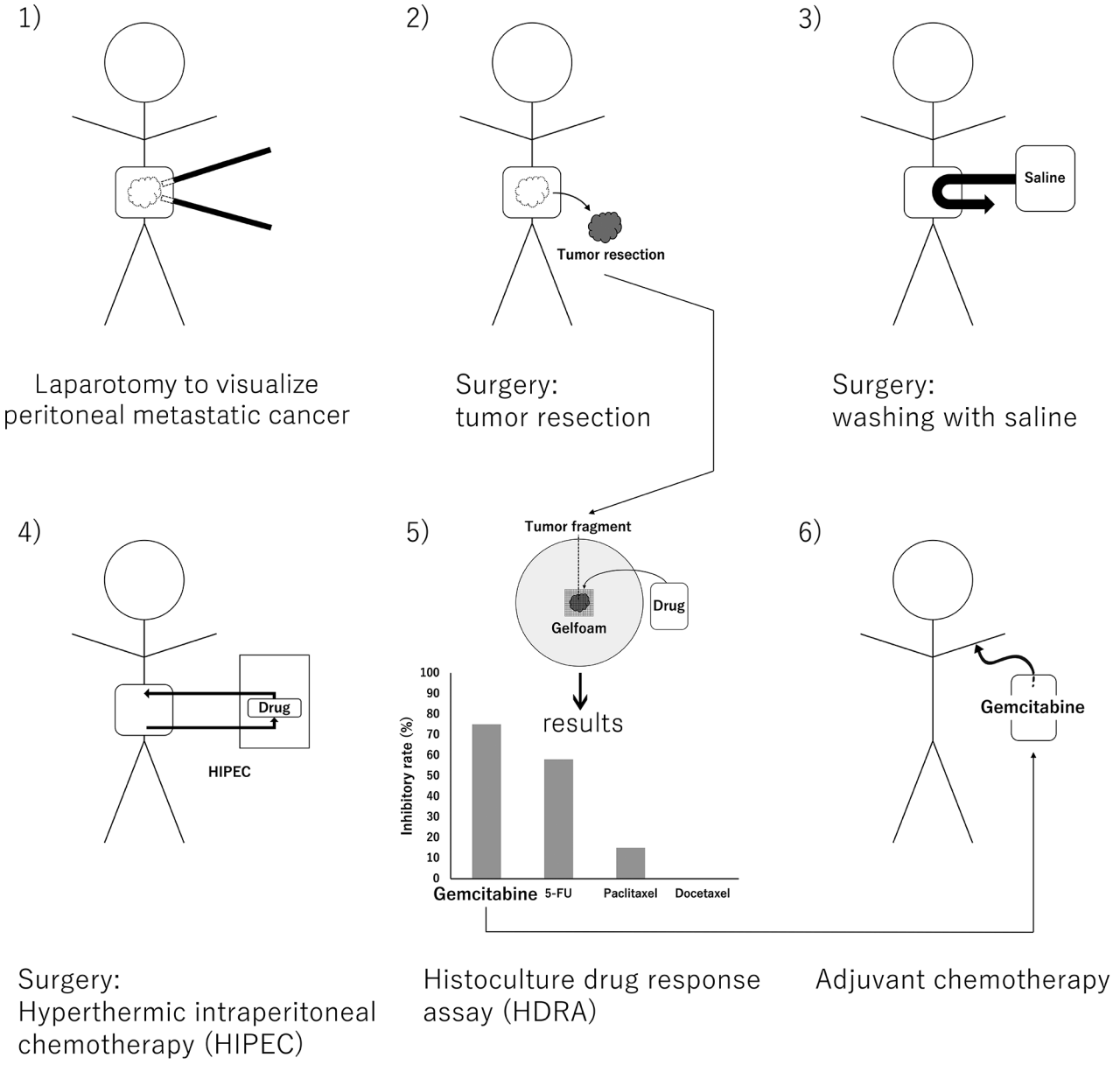

Figure 1. *Effective treatment of peritoneal metastatic cancer.*

A fragment of the resected peritoneal tumor was placed in 3-D histoculture and tested for drug response in the HDRA. Various drugs were added to the 3-D histocultures to determine which drugs are effective against the tumor (19-23). In the present case, the HDRA showed that gemcitabine was the most effective of six drugs tested, with an inhibitory rate of 70% compared to 58% for 5-FU. Paclitaxel and docetaxel were ineffective. The patient was treated with systemic gemcitabine and was alive 18 months after the peritonectomy, an unexpected result.

Discussion

PACC cells do not invade into the subperitoneal tissue (24). Therefore, the peritoneal metastasis of PACC could be removed by peritonectomy. Treatment with gemcitabine, identified as effective by the HDRA, most probably eradicated minimal residual disease (MRD) remaining after peritonectomy and HIPEC using gemcitabine and docetaxel.

What we have learned from the present case is that peritoneal metastatic cancer is potentially curable with the following: 1) Laparotomy for identifying the extent of peritoneal metastases which is necessary since current imaging technology can not sufficiently detect tumors in the peritoneum; 2) Peritonectomy to remove all macro metastases; 3) Extensive intraoperative peritoneal washing with saline; 4) HIPEC; and 5) The HDRA to identify the most effective drug for adjuvant chemotherapy (Figure 1).

These procedures can be individualized for the patient's cancer. The HDRA is most critical for individualization and potential cure. The present perspective is an example of a potential cure for stage IV cancer and the present principle can be applied to patients with peritoneal metastasis and other stage IV cancers, especially for those cancers with no consensus for treatment (25). In addition patient derived orthotopic xenograft (PDOX) mouse models can be established from the resected tumor for anti-metastatic drug screening (26). An additional treatment strategy is to add methionine restriction (MR) to the present treatment protocol for peritoneal metastasis (27).

Conflicts of Interest

The Authors declare no competing interests regarding this work.

Authors' Contributions

YA was a major contributor to writing the manuscript and RMH revised the article. YY established the clinical strategy and performed the surgery. KM, BMK, JSK, NY, KH, ShM, KI, TH, SeM, HT and SD critically read and approved the final article.

Acknowledgements

This paper is dedicated to the memory of A.R. Moossa, MD, Sun Lee, MD, Richard W. Erbe, MD, Professor Gordon H. Sato, Professor Li Jiaxi, Masaki Kitajima, MD, Shigeo Yagi, PhD, Eugene P. Frenkel, MD, John Medelsohn, MD, Professor Lev Bergelson, Professor Sheldon Penman, Professor John R. Raper and Joseph Leighton, MD.

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