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Case Report

Cure of unresectable, locally advanced pancreatic cancer after multidisciplinary therapy

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ABSTRACT

The treatment of unresectable, locally advanced pancreatic cancer (ULAPC) is highly challenging as it is considered to be an incurable disease. Our previous studies demonstrated that the combination of gemcitabine, oxaliplatin and 46-h infusion of fluorouracil (5-FU) and leucovorin, the GOFL regimen, is a promising, well-tolerated triplet regimen for locally advanced and recurrent/metastatic pancreatic cancer. Herein, we report a case of ULAPC who remained alive and disease-free for more than five years after a successful, multidisciplinary approach consisting of a 9-month course of induction GOFL, followed by gemcitabine-based concurrent chemoradiotherapy (CCRT) and maintenance GOFL, and subsequently radical R0 resection. This case highlights that prolonged multi-agent chemotherapy with consolidation CCRT can be used to select the patients with ULAPC who may be potential candidates for curative-intent resection, and ultimately even lead to a cure for ULAPC.

1. Introduction

Pancreatic cancer is a highly lethal disease associated with a high rate of cancer-related deaths worldwide, including Taiwan. Its poor prognosis clearly reflects the advanced stage of disease at diagnosis in most patients, and only 20% of newly diagnosed patients are classified as having resectable disease.[1] Because of the technical difficulty in achieving complete resection and the subsequent poor clinical outcomes after the primary operation, non-metastatic pancreatic cancers that directly extend to the celiac axis and superior mesenteric artery regardless of the evidence of non-obstructive invasion of the superior mesenteric-portal vein confluence are defined as a single disease group, termed "locally advanced pancreatic cancer (LAPC)".[2,3] The PRODIGE/ACCORD and MPACT trials only included patients with metastatic diseases to evaluate the therapeutic efficacies of FOLFIRINOX and nab-paclitaxel/gemcitabine treatment compared to gemcitabine alone, respectively.[4,5] Before these trials, patients with LAPC were frequently included into clinical trials to evaluate the efficacies of primary gemcitabine-based chemotherapy for advanced/metastatic pancreatic cancer.[6]

With the recognition of LAPC as a systemic disease and the emergence of frontline chemotherapy-based multidiscipline treatment for patients with LAPC, it appeared that the clinical outcomes of the patients could be significantly affected by the extent of vascular involvement of their LAPC. Accordingly, it has recently been proposed that LAPC should be categorized into borderline resectable pancreatic cancer (BRPC) and unresectable, locally advanced pancreatic cancer (ULAPC) based on the extent of vascular involvement.[7–9] Two recent reports from John Hopkins Hospital (JHH) and the GERCOR LAP07 study investigated the clinical outcomes of patients with LAPC receiving neoadjuvant chemotherapy (mainly gemcitabine-based regimens) with or without chemoradiotherapy (CCRT) between 2007 and 2008 and 2011, and reported a median overall survival of 15.5 months in 72 patients with BRPC and 12.8 months in 442 patients with ULAPC, respectively.[10,11] In comparison, 41.7% (30/72) of the patients in the JHH series and 4.1% (18/442) of the patients in the LAP07 study who underwent curative resection had a median overall survival of longer than 24 months. These findings support the distinction of BRPC and ULAPC in recent pancreatic cancer management

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guidelines,[12–14] and the very rare occurrence of ULAPC converting into resectable disease in the era of gemcitabine as the standard of care for locally advanced or metastatic pancreatic cancer. Therefore, patients with non-metastatic ULAPC are generally considered to be incurable at diagnosis, and systemic chemotherapy remains the standard of care for palliative treatment.

Due to the modest activity of gemcitabine either alone or in combination with 5-FU,[15] our institute has engaged in the development of a triplet chemotherapy regimen consisting of gemcitabine, oxaliplatin and leucovorin-modulated fluoropyrimidine for patients with advanced pancreatic cancer since the early 2000s. After a phase I study to determine the feasibility and maximum tolerated dose of oxaliplatin,[16] we evaluated the therapeutic efficacy of a triplet chemotherapy regimen consisting of a fixed-dose rate infusion of 800 mg/m^2 gemcitabine followed by a 2-h infusion of 85 mg/m^2 oxaliplatin and then a 48-h infusion of 5-FU and leucovorin (3000 mg/m^2 and 300 mg/m^2, respectively), termed the GOFL regimen, in patients with locally advanced/metastatic pancreatic cancer.[17] The overall objective response rate (ORR) and median overall survival (OS) of the 45 intent-to-treat patients were 33.3% (95% CI 21.4–48.0) and 8.7 (95% CI, 6.1–11.3) months, respectively. In post hoc analysis, the median OS of the nine patients with LAPC was 15.9 (95% CI 11.3–20.5) months. Based on these findings, we evaluated the efficacy of a 3-month course of induction GOFL followed by gemcitabine-based (CCRT) in patients with LAPC in the Taiwan Cooperative Oncology Group 1204 (TCOG-1204) study.[18] The median time to progression (TTP) and median OS of the 30 patients who completed 3 months of the GOFL regimen and subsequent CCRT were 14.7 months (95% CI 11.8–17.6) and 18.3 months (95% CI 17.1–19.6), respectively. Thereafter, a multidiscipline approach with first-line GOFL became our favored clinical practice for patients with ULAPC outside clinical trials before the approval of new agent(s) for pancreatic cancer in Taiwan.

In this study, we describe a case of ULAPC who was cured after successful multidiscipline treatment including a 9-month course of induction GOFL, followed by gemcitabine-based CCRT and maintenance GOFL, and then radical R0 resection.

2. Case report

This 55-year-old woman had a history of hypertension and hepatitis C. In late August 2010, she presented with the complaints of severe epigastralgia radiating to her back, body weight loss (about 8 kg in 1 month), and poor appetite for 2 months before being referred to our hospital. Initial laboratory examinations revealed anicteric, and previously unrecognized diabetes mellitus. Her serum CA 19-9 level was about 1800 U/ml. A computed tomography (CT) scan of her abdomen revealed a hypodense mass lesion (about 4.0 cm in diameter) located in the pancreatic body encased in a branch of the celiac trunk, and abutting the superior mesenteric artery (SMA) by > 180° without deformity, and several non-enlarged regional lymph nodes were also found (Fig. 1). A histological examination of a CT-guided biopsy was compatible with adenocarcinoma. Serial imaging studies for staging did not identify any distant metastases. Taken together, the final clinical stage was T4NXM0, Stage III, ULAPC.

The patient began six courses of induction GOFL therapy from early September 2010 to December 2010. The GOFL regimen consisted of gemcitabine at a fixed-dose rate (10 mg/m^2/min) and a dose of 800 mg/m^2 on D1, followed by oxaliplatin at a dose of 85 mg/m^2 by 2-h infusion on D1, and then 48-h infusion of fluorouracil (3000 mg/m^2)/leucovorin (150 mg/m^2) on D1-2 biweekly.[16,17] She tolerated the GOFL regimen well except for nausea (grade I), vomiting (grade I), diarrhea (grade I), and oral mucositis (grade II). Her serum CA 19-9 level decreased to 361.2 U/ml approximately 2 months after initiating GOFL induction therapy, and a follow-up CT scan of her abdomen showed stable disease 2 months after GOFL therapy (Fig. 2B). She subsequently received concurrent gemcitabine-based CCRT (total of 50.4 Gy in 28 fractions) with gemcitabine (400 mg/m^2 weekly) from late December 2010 to early February 2011. After completing CCRT, a follow-up CT scan of her abdomen showed that the tumor had shrunk by approximately 20% compared to the size at the initial diagnosis (Fig. 2C), along with a decrease in her serum CA 19-9 level to 63.77 U/ml.

A 3-month course of maintenance GOFL was initiated following CCRT, during which she experienced the mild treatment-related adverse effects of leukopenia (grade I), anemia (grade I), and peripheral sensory neuropathy (grade I). No dose interruptions or reductions occurred during the maintenance course. After completing maintenance GOFL, a follow-up CT scan of abdomen revealed that the tumor had shrunk to about 2.9 cm in diameter, and now loosely abutted the SMA (Fig. 2D). In addition, her serum CA 19-9 level had decreased to 41.3 U/ml. Subsequently, subtotal pancreatectomy, splenectomy, superior mesenteric vein (SMV) partial excision, and lymphadenectomy were performed, and a histologic examination of the resected specimens revealed residual adenocarcinoma infiltrating into pancreatic parenchyma, with no evidence of angiolymphatic invasion, although perineural invasion was found. Moreover, all resection margins were free from malignancy (R0 resection), and all dissected lymph nodes and spleen were also negative for malignancy. There were no postoperative complications. Two months after subtotal pancreatectomy, an abdominal CT scan showed no evidence of local or regional recurrence or distant metastases (Fig. 3A). Four months after surgery, her serum CA19-9 level was 6.46 U/ml. As of writing, the patient is still alive and remains pancreatic cancer-free without any recurrence or metastasis for more than five years since mid-2011 (Fig. 3B).

3. Discussion

The current report describes the conversion of unresectable, non-metastatic LAPC into resectable disease after a successful multidisciplinary approach, which was finally cured by radical R0 resection. Although this case illustrates the very rare occasion of converting ULAPC into resectable disease in the LAP07 study,[11] we would like to emphasize that the emergence of more effective multi-agent chemotherapy and multi-discipline approaches may increase the likelihood of a cure in patients with non-metastatic ULAPC at diagnosis.

Recent randomized phase III trials have demonstrated the survival benefits of either FOLFIRINOX or nab-paclitaxel/gemcitabine combination compared to gemcitabine alone in patients with metastatic pancreatic cancer,[4,5] however such data have not previously been reported in patients with BRPC/ULAPC. One recent patient-level meta-analysis showed that first-line FOLFIRINOX with and without consolidation (chemo)-radiotherapy resulted in a 28.2% resection rate, 24.2 (95% CI 21.7–26.8) months of median OS (95% CI 42.9–57.4), and a 2-year survival rate of 50.1% in 315 patients with ULAPC from 11 retrospective studies.[19] The survival outcomes were close to those of patients who received adjuvant gemcitabine after curative resection in modern adjuvant trials including the JASPAC01 and ESPAC4 studies.[20,21] Although the results shed light on the activity of modern multi-agent combinations to provide the possibility of a cure for a certain proportion of patients with ULAPC, the safety profile and patient compliance remained major concerns for the application of FOLFIRINOX in the patients with ULAPC, as it does in patients with metastatic diseases. For example, despite the primary prophylactic use of granulocyte-colony stimulating factor, 4/22 (18%) patients with ULAPC experienced grade 3–4 neutropenia, and 32% of the patients required

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