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Case Report

Consistent Response on Challenge and Rechallenge of Liposomal Irinotecan in a Patient with Metastatic Pancreatic Adenocarcinoma Previously Treated with Gemcitabine plus Nab-Paclitaxel: A Case Report

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Pancreatic cancer · Liposomal irinotecan · Chemotherapy · Metastasis · Neoadjuvant chemotherapy · Case report

Abstract
Approximately 80% of pancreatic cancer is diagnosed at an advanced stage, due to lack of or vague symptoms when the cancer is still localized, leading to a high mortality rate. Known risk factors for developing pancreatic cancer are family history, obesity, type 2 diabetes, and alcohol and tobacco use. There has been a remarkable development in diagnosis modalities and molecular testing, but early detection is still infrequent. The majority of clinical trials have not shown significant efficacy in pancreatic cancer, and treatment strategy remains limited. Additional prognostic factors should be highlighted to obtain appropriate treatment options, including precision medicine, and improve survival outcomes. After the PRODIGE study in 2011 and the MPAC trial in 2013, a new drug (liposomal irinotecan; Onivyde ®) appeared in the strategy, especially after failure of gemcitabine-based treatment. In 2016, the NAPOLI-1 trial showed evidence of the efficacy of the liposomal irinotecan combination (liposomal irinotecan +5-fluorouracile + folinic acid); now, it is considered the standard treatment for relapsing patients. Since NAPOLI-1, real-world data have provided similar results. Herein, we report the story of

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a 61-year-old woman who was treated with liposomal irinotecan combination (nal-IRI/5-FU/LV) for 8 months with good surgical response, but treatment was discontinued due to economic burden. After the start of treatment (or 1? cycle of liposomal irinotecan treatment), the patient was in a better condition. The liver metastases had disappeared. The combination with liposomal irinotecan was re-administered with patient's approval. Upon rechallenge with the liposomal irinotecan combination, she showed a partial response, and the treatment was given for 7 months. In this report, we tried to identify the prognostic factors leading to the efficacy of the liposomal irinotecan combination.

Introduction

Pancreatic adenocarcinoma (PAC) is considered a lethal malignancy due to high mortality and morbidity, as it is the fourth leading cause of death in the USA and the fifth in Korea [1–3]. The most important prognostic factor is the stage at which the patient is diagnosed. In case of earlier detection, the main cure for PAC is surgical resection, followed by chemotherapy, radiotherapy, and other locoregional therapies, customized for the patient condition and clinical course [4]. In most cases, the patients are diagnosed with metastatic pancreatic cancer (mPAC), even with development of new diagnosis modalities [5].

Recently, a lot of clinical trials have been conducted with interest by physicians who are treating pancreatic cancer, as treatment options are still limited. In spite of these efforts to develop new drugs, including immune-oncologic medicines, all trials failed to show clinical efficacy. Previously, systemic chemotherapy combinations, including FOLFIRINOX (5-fluorouracil, folinic acid, leucovorin, irinotecan, and oxaliplatin) supported by the PRODIGE study and gemcitabine plus nab-paclitaxel demonstrated by the MPAC trial, remained the main treatments for patients with advanced disease, which was before the NAPOLI-1 trial published in 2016 [6–8].

In second-line treatment for mPAC, the randomized phase III NAPOLI-1 trial provided evidence for the survival benefit of liposomal irinotecan combination after failure of previous gemcitabine-based regimen compared with 5-fluorouracil, folinic acid, and leucovorin [9]. With these results and additional reports from real-world evidence, the NAPOLI regimen (liposomal irinotecan, 5-fluorouracil, and folinic acid) is now considered a standard second-line treatment for mPAC [6].

Usually, later lines of treatment give a shorter survival expectation, since mPAC patients experienced disease progression, exposure for cytotoxicity causing various adverse events (AEs), and then inducing generalized weakness with a decrease in performance status. Here, in second line after failure of gemcitabine plus nab-paclitaxel, the patient showed prolonged drug response and rechallenge response with the NAPOLI regimen. This kind of case with rechallenge has not been previously reported in the literature. This article reports the detail of this patient's experience.

Case Report

A 61-year-old woman was admitted to the hospital with jaundice as a main symptom in November 2018. Jaundice aggravation was observed over a month ago, and the patient started to feel itchy over her whole body. Repeated chill also started with the itching, making her go to the Emergency Unit of another hospital. After examination at the hospital, she was

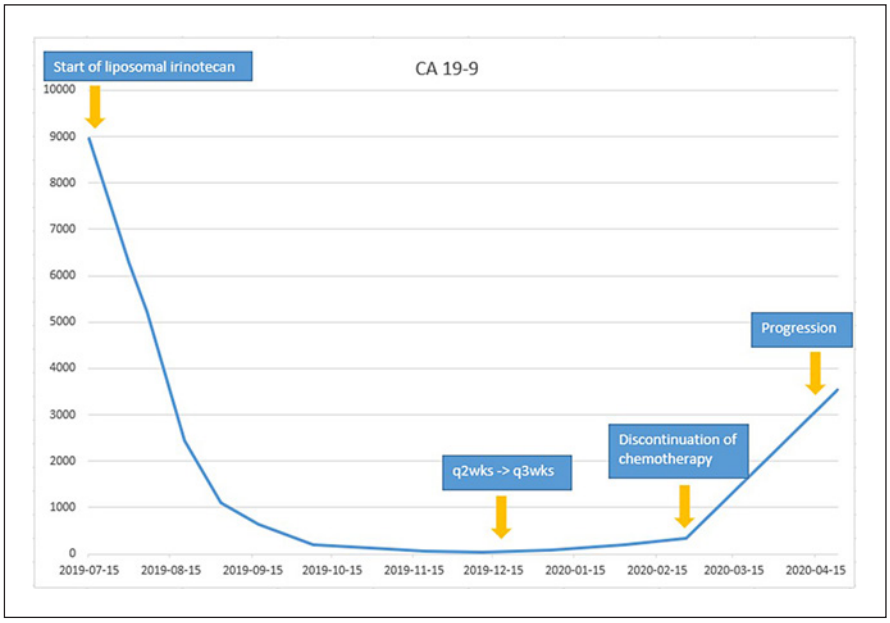

Fig. 1. The graph shows serum concentration change of CA 19-9 in the period of first challenge of liposomal irinotecan with 5-fluorouracil and folinic acid. At the second challenge of the regimen, the concentration showed constantly over 10,000 U/mL.

transferred to the tertiary center (Dongguk University Ilsan Hospital) for specific examinations and tests.

There was no other medical history other than hypertension. Regarding family history, her mother died of pancreatic cancer in her 70s. The patient's Eastern Cooperative Oncology Group (ECOG) Performance Status was 1, and body mass index was 24.7 kg/m^2. In the blood test, the total bilirubin was 6.3 mg/dL, AST 190 IU/L, ALT 287 IU/L, ALP 441 IU/L, and CA 19-9 8,840 U/mL. At enhanced-contrast computed tomography (CT), 1.4 cm of mass was observed in the pancreas uncinated process, and multiple liver metastases were found upon magnetic resonance image (MRI). A biopsy was conducted using endoscopic ultrasound and confirmed as pancreatic ductal adenocarcinoma with multiple liver metastases.

The treatment of gemcitabine plus nab-paclitaxel was initiated as palliative first-line chemotherapy, which stabilized the disease after 2 cycles, but a disease assessment after 4 cycles confirmed progression of the disease. In the blood test at this time, AST was 22 IU/L, ALT 8 IU/L, ALP 59 IU/L, CA 19-9 8,961 U/mL, neutrophil-to-lymphocyte ratio 1.94, and serum albumin 4.6 g/dL. The patient and her family members discussed a potential second-line chemotherapy option, and it was decided to administer the NAPOLI regimen: liposomal irinotecan 70 mg/m^2, 5-FU 400 mg/m^2 IV bolus, 2,400 mg/m^2 continuous infusion bi-weekly and continued for 6 months without disease progression or dose adjustments.

Grade 1 diarrhea was reported, but it was controllable with anti-diarrhea medicine. There were no other specific AEs described. A fever after 2 cycles of treatment was reported, but it was confirmed to be obstructive cholangitis, not febrile neutropenia, which improved after pancreatic endoscopy and antibiotic treatment. Subsequently, it was confirmed that there were no special side effects to consider dose reduction, dose modification, transient interruption, or delay of treatment during liposomal irinotecan treatment. CA 19-9 decreased dramatically, and the liver metastases disappeared rapidly as confirmed in CT controls (Fig. 1, 2).

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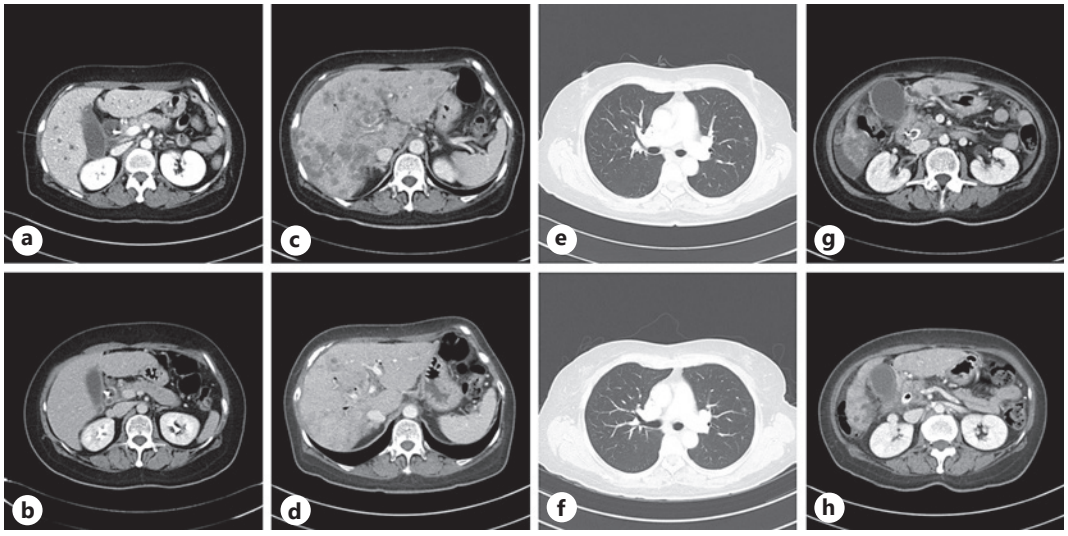

Fig. 2. Contrast-enhanced CT images of the abdomen and high-resolution CT images. **a** Before the treatment with liposomal irinotecan. Primary origin mass of pancreatic cancer and multiple liver metastasis. **b** After 5 months of liposomal irinotecan. Decreased size of primary origin and disappeared liver metastasis. **c–e** Before the rechallenge with liposomal irinotecan. Extensive multiple liver metastasis, ascites, increased size of origin mass, and lung metastasis. **f–h** Six weeks after rechallenge with liposomal irinotecan. Improved multiorgan metastasis and decreased origin mass size.

The patient felt burdened by the cost of cancer treatment (nonreimbursed), and the CT showed only the primary mass in the pancreas with decreased size, so surgery was considered as another option. MRI and positron emission tomography-CT showed that there was no other disease other than the primary tumor of the pancreas.

In January 2020, a multidisciplinary board discussion was taken with other departments, considering surgery. The general surgery team agreed that the patient cancer lesion looked resectable, thereby surgery was considered. After reflection and discussions, the patient and family decided to refuse surgery with the reason of psychological and health burden of this intervention. Finally, the dose interval of chemotherapy was increased to reduce the treatment cost, until the patient was lost to follow-up after February 26, 2020.

For 2 months, she did not come back to the hospital. Two months after the suspension of the treatment, a disease aggravation was newly observed and extensive liver metastases confirmed, when she came to the hospital with symptoms. Antibiotics had to be considered for a hepatic abscess accompanied by biliary inflammation after the first month. For 3 months, best supportive care was given. The patient wanted to resume chemotherapy after the end of antibiotic treatment, so the patient and physicians discussed possible options. At that time, there was no ongoing clinical trial in the center, and FOLFIRINOX was not a careful option due to the regimen toxicity and her general condition, so it was decided to rechallenge with the NAPOLI regimen.

For 7 months of rechallenge (July 2020–January 2021), the treatment was again efficient, and the CT showed a reduction in the legions in the pancreas, lungs, and peritoneum. After 11 cycles of administration with prolonged dose interval due to her condition, CT confirmed progression of the disease and chemotherapy was stopped.

In total, she responded to the liposomal irinotecan combination for 7 months with 13 cycles during the first challenge and 7 months with 10 cycles during the rechallenge. Finally, she died 2 months after chemotherapy discontinuation. The overall survival was 20 months, and progression-free survival in the rechallenge period was 7 months.

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Discussion

In several real-world evidence reports, median overall survival (mOS) and median progression-free survival (mPFS) were in line with the NAPOLI-1 trial (mOS 6.2 months and mPFS 3.2 months). There is only one case report showing prolonged response to liposomal irinotecan [10]. In this case report, the patient received liposomal irinotecan for 51 weeks with 25 cycles as third-line treatment, after 2 months of FOLFIRINOX in first line and 2 months of gemcitabine plus nab-paclitaxel in second line. However, this current case report is the first to report on rechallenge with liposomal irinotecan (challenge–discontinuation of treatment–rechallenge). In total, 14 months of second-line liposomal irinotecan treatment with 23 cycles were given, with 20 months of overall survival obtained.

At the analysis of long-term survivors in NAPOLI-1, 29 (25%) in the NAPOLI arm and 20 (13%) in the fluorouracil-based control arm were alive (and not censored) after 1 year. Among long-term responders, median OS was 19.1 (95% CI: 15.3–21.3) and 23.4 (95% CI: 16.1–33.3) months in the NAPOLI arm and control arm, respectively; median PFS was 9.9 (95% CI: 7.0–14.2) and 8.1 (95% CI: 2.7–13.8) months in the NAPOLI arm and control arm, respectively [11]. At the analysis, patients in the NAPOLI arm with long-term survival were more likely to be aged ≤65 years; have Karnofsky performance status ≥90, NLR ≤5, and CA19-9 level <59× the upper limit of normal; and be less likely to have liver metastases [11]. On the other hand, other prognostic factors were identified at the nomogram analysis. Baseline albumin concentration ≥4 g/dL and body mass index ≥25 kg/m^2 were suggested [12]. The patient of this case report had good prognostic factors such as good performance status, NLR ≤5, and normal albumin concentration.

Liposomal irinotecan seems to be beneficial for Asian patients when it comes to survival and diarrhea. In the Asian subgroup analysis of NAPOLI, the mOS of Asian patients was 8.9 months and the mPFS was 4.0 months [13]. In terms of treatment emergent AEs leading to any dose modification, Asians showed numerically higher neutropenia (87.8%), compared to the full safety analysis set (45.3%). On the other hand, dose modification due to diarrhea was 0.3% in Asians and 15.4% in the full safety analysis set [13]. This ethnic difference is sometimes explained by the delayed metabolism of liposomal irinotecan, thereby tumor-associated macrophage uptake and activation of the drug leading to an increase in local SN-38 concentrations [14]. The patient showed one episode of grade 1 diarrhea, which was easily managed. There was no neutropenia observed. Major morbidity causing dose modification was cholangitis (twice) or associated liver abscess with fever.

The patient demonstrated prolonged response with long-term survival and consistent response with stable status with second-line treatment using the NAPOLI regimen; lack of patient's molecular biological information remains as the limitation. Pancreatic cancer is a well-known dense stromal tissue malignancy, which explains the difficulty in anticancer therapy penetration and many clinical trial failure. However, several molecular factors are under investigation [15]. The POLO trial, which involved the identification of germline BRCA mutations and used a targeted therapy, proved to be effective, and such approaches are worth further exploration. With this reason and expensive cost, molecular subset diagnosis for genomic profiling, such as next-generation sequencing in pancreatic cancer, is still under the performance. In the perspective, precision medicine will give the more customized treatment option and prognostic expectation. In this circumstance, for patients with unresectable pancreatic cancer, FOLFIRINOX or gemcitabine plus nab-paclitaxel regimens were shown to achieve the longest mOS in first line and the NAPOLI regimen shows the strongest evidence in second line, after failure of a gemcitabine-based therapy.

Conclusion

In metastatic pancreatic cancer, the NAPOLI regimen is the most approachable treatment at second line, after failure with gemcitabine-base regimen. The regimen showed long-term survival and consistent response at rechallenge, without serious AEs. At the vague condition for strong prognostic factors including genomic profiling subsets, evidence with clinical trial can lead to continuum of care for longer survival benefit.

Statement of Ethics

This case report was reviewed and approved by the Institutional Review Board, Dongguk University Ilsan Hospital, Dongguk University College of Medicine (DUIH 2021-09-004). The IRB approved a waiver of informed consent process.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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We certify that the authors listed here have no affiliations with or involvement in any organizations and/or any financial interests.

Author Contributions

Hyun Jung Lee and Dalyong Kim contributed to conceptualization, methodology, reviewing and editing, and supervision. Seong-Ryong Kim contributed to data curation and writing – original draft preparation.

Data Availability Statement

Data are not publicly available by the Personal Information Protection ACT of Korea.

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