Prolonged response to liposomal irinotecan in a patient with stage IV pancreatic/bile duct cancer previously treated with FOLFIRINOX and gemcitabine plus nab-paclitaxel

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ABSTRACT

At 9%, and 2% when diagnosed at advanced stage, the 5-year relative survival rate for pancreatic ductal adenocarcinoma (PDAC) is the lowest of any cancer. The currently approved treatment options for metastatic PDAC in the United States are FOLFIRINOX [irinotecan–fluorouracil (5FU)–leucovorin (LV)–oxaliplatin], gemcitabine–nab-paclitaxel, and liposomal irinotecan plus 5FU–LV.

Liposomal irinotecan is a novel formulation of irinotecan encapsulated within a lipid bilayer, which favours local metabolic activation. The NAPOLI-1 trial demonstrated the efficacy of liposomal irinotecan in combination with 5FU and LV for the treatment of advanced PDAC after progression on gemcitabine-based chemotherapy. The 1-year survival in those patients was 25%; however, none had had irinotecan-refractory disease before treatment with liposomal irinotecan. Furthermore, the U.S. National Comprehensive Cancer Network guidelines recommend liposomal irinotecan plus 5FU–LV in patients who have received prior fluoropyrimidine-based therapy if no prior irinotecan therapy has been given. Here, we report a male patient with stage IV cancer of pancreas or bile duct (site unconfirmed) who experienced a prolonged (51 weeks) response to liposomal irinotecan plus 5FU–LV despite prior disease progression on irinotecan.

Several factors have previously been associated with long-term survival in patients receiving liposomal irinotecan therapy: no prior irinotecan-based chemotherapy, high Karnofsky performance status score, age 65 years or less, serum carbohydrate antigen 19-9 less than 59 U/mL, neutrophil-to-lymphocyte ratio 5 or less, and absence of liver metastasis. The patient in the present report had none of those characteristics indicative of long-term survival, except his age at diagnosis—47 years.

Key Words Pancreatic cancer, bile duct cancer, liposomal irinotecan, irinotecan, FOLFIRINOX, chemotherapy

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INTRODUCTION

Cancer is the 2nd leading cause of death in the United States, and of all cancers diagnosed, 7% are pancreatic¹. It is estimated that, in 2019, 56,770 cases of pancreatic ductal adenocarcinoma (PDAC) will occur in the United States and that 45,750 of them will result in the death of the patient¹. Pancreatic cancer is most frequent in individuals more than 40 years of age, with a slightly higher prevalence in men^{1–3} and a significantly higher incidence in the African American than in the white American population^{1,3,4}. Risk factors for the disease include genetics, cigarette smoking, and increased body mass index².

Early detection of the signs and symptoms of PDAC is vital for increasing the survival rate; however, symptoms can be mild and undetectable or late in onset. For that reason, the 5-year relative survival rate for PDAC is the lowest of any cancer at 9%—and 2% when diagnosed at an advanced stage¹.

In the United States, the standard first-line drug therapy for metastatic PDAC is FOLFIRINOX [irinotecan–fluorouracil (5FU)–leucovorin (LV)–oxaliplatin]^{2,3}. Gemcitabine–nab-paclitaxel is also recommended as both first- and second-line treatment, depending on factors such as the patient's performance status and comorbidity profile^{2,3}. A phase III trial, NAPOLI-1, provided evidence for

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the use of liposomal irinotecan (Onivyde; Ipsen, Paris, France) as second-line treatment for metastatic PDAC after initial gemcitabine-based treatment⁵. This novel formulation of irinotecan is encapsulated within a lipid bilayer, which favours local metabolic activation. The NAPOLI-1 study resulted in approval of the formulation by the U.S. Food and Drug Administration. Liposomal irinotecan plus 5FU-LV is recommended in clinical guidelines for treatment of metastatic PDAC after gemcitabine treatment^{2,3}.

Here, we report a male patient with stage IV cancer of pancreas or bile duct (site unconfirmed) and prior disease progression on irinotecan (as part of FOLFIRINOX) who experienced a prolonged (51-week) response to liposomal irinotecan plus 5FU-LV.

CASE DESCRIPTION

A 47-year old African American man with a history of cigarette smoking and alcohol consumption and a body mass index of 22.19 kg/m² reported to Mitchell Cancer Institute at The University of South Alabama on 21 September 2017 for a second opinion regarding stage IV cancer of pancreas or bile duct previously treated at another cancer centre.

On 17 March 2017, the patient had presented to his primary care physician with abdominal pain, nausea, diarrhea, and weight loss. Computed tomography (CT) imaging of abdomen and pelvis showed diffuse extensive hepatic lesions compatible with metastasis. An ultrasound-guided liver biopsy was performed, and histopathology showed an adenocarcinoma whose immunophenotype was positive for cytokeratin 7 and negative for cytokeratin 20, CDX-2, and TTF-1. Those findings were suggestive of a tumour of pancreaticobiliary or upper gastrointestinal origin.

Molecular analysis of the tumour by next-generation sequencing using the FoundationOne CDx gene panel (Foundation Medicine, Cambridge, MA, U.S.A.), which consists of 315 cancer-related genes, showed genomic alterations significant for amplification of genes in signal transduction pathways (*PI3K*, *Akt*, *FGF*, and *IKBKE*), cell cycle regulation [*CCND1*, *MDM4*, and *CDKN2A* (p16)], and protein ubiquitination (*CUL3*).

To visualize the upper gastrointestinal tract, the patient underwent esophagogastroduodenoscopy, but no primary tumour was visualized. Colonoscopy was performed at the same time and was unremarkable. Endoscopic ultrasonography showed no focal pancreatic mass, but showed peri-pancreatic lymphadenopathy. Carbohydrate antigen 19-9 (CA19-9) was elevated at more than 20,000 U/mL (normal: 0.0–37.0 U/mL).

The case was discussed at the multidisciplinary tumour board, and the diagnosis of stage IV cancer of pancreas or bile duct with metastasis to the liver was made. On 20 April 2017, at the first cancer centre, the patient received first-line treatment with FOLFIRINOX, completing 3 cycles, after which, on 21 May 2017, he experienced severe abdominal pain secondary to development of a pelvic abscess. The abscess was drained on 2 June 2017, and the patient improved. Unfortunately, however, on 28 June 2017, before restarting FOLFIRINOX, the patient showed radiologic evidence of disease progression in the liver, assessed by the Response Evaluation Criteria in Solid Tumors.

In July 2017, the patient was started on second-line treatment with gemcitabine–nab-paclitaxel. Clinically, the patient was not doing well and progressively worsened. He started to have abdominal distension from ascites that required periodic (more than once-weekly) paracentesis. On 28 August 2017, radiologic evidence showed large-volume ascites despite a slight improvement to stable liver metastasis. The patient was advised to enrol in hospice.

The patient then came to Mitchell Cancer Institute for a second opinion, and on 4 October 2017, he was started on liposomal irinotecan 70 mg/m², plus 5FU 2400 mg/m² and LV 400 mg/m² (dose and administration per product label). Clinically, he improved, and the need for paracentesis became less frequent. After a few months, paracentesis was no longer needed. After 4 cycles, radiologic evidence of stable disease was observed, and subsequent images showed interval-decreased amounts of ascites.

Contrast-enhanced CT imaging of the patient's abdomen on 22 November 2017 [Figure 1(A)] showed multiple hepatic metastases in an atrophic liver, with a dominant conglomeration in the right lobe and large-volume ascites. Contrast-enhanced CT imaging on 5 July 2018 showed multiple hepatic metastases, but with decreased size of the dominant right hepatic mass indicative of partial response, with the right lobe further atrophied and the ascites volume also decreased [Figure 1(B)].

Unfortunately, contrast-enhanced CT imaging of the patient's abdomen performed on 26 September 2018 after 51 weeks and 25 cycles of liposomal irinotecan revealed disease progression [Figure 1(C)]. At that time, an ultrasound-guided liver biopsy was performed and showed moderately differentiated adenocarcinoma with an immunophenotype identical to the tumour biopsied in 2017, and compatible with pancreaticobiliary or upper gastrointestinal origin.

Analysis of the recurrent tumour by next-generation sequencing with the MI Tumor Seek 592-gene panel (Caris Life Sciences, Irving, TX, U.S.A) revealed pathogenic mutations in *KRAS*, *SMAD4*, *TP53*, and *APC*. The tumour was microsatellite-stable, but had an intermediate tumour mutational burden (14 mutations/Mb). The patient received an additional 3 cycles of liposomal irinotecan plus 5FU-LV while waiting for pembrolizumab to be provided for compassionate use.

The patient switched to pembrolizumab (200 mg) in November 2018. After completion of 2 cycles of pembrolizumab, CT imaging indicated disease progression, with increased size and distribution of hepatic lesions. Because the patient was doing well, those results were considered possibly, although unlikely, to be a result of pseudoprogression. In total, the patient received 4 cycles of pembrolizumab before hospice referral in February 2019. The patient died shortly thereafter.

DISCUSSION

With more than 50% of PDACs being diagnosed at a late stage, the 5-year survival for advanced PDAC is only 2%^{1,6}. The years since about 2010 have witnessed the development of 3 new and effective combination chemotherapy regimens: FOLFIRINOX, gemcitabine–nab-paclitaxel, and liposomal irinotecan plus 5FU-LV^{5,7,8}. The optimal approach

FIGURE 1 Contrast-enhanced computed tomography imaging of abdomen. (A) Imaging on 22 November 2017 shows multiple hepatic metastases in an atrophic liver, with a dominant conglomeration in the right lobe. Large-volume ascites is also noted. (B) Imaging on 5 July 2018 again shows multiple hepatic metastases, with decreased size of the dominant right hepatic mass indicative of partial response. The right lobe has further atrophied. Ascites volume is decreased. (C) Imaging after 52 weeks and 25 cycles of treatment with liposomal irinotecan plus 5-fluorouracil–leucovorin (26 September 2018) again shows multiple hepatic metastases, with a new segment IVa mass indicative of disease progression.

to sequencing the available treatment options has yet to be defined. In clinical practice, sequencing is usually a function of physician comfort level and experience, and of patient-specific factors such as age, performance status, and adequate organ function. Predictive molecular biomarkers that are clinically relevant—such as microsatellite instability, mutations in *BRCA1/2*, and *NTRK* gene fusion—can be adopted in the clinic, but are found in a small proportion of patients⁹.

Liposomal irinotecan, a novel formulation of irinotecan encapsulated within a lipid bilayer, favours local metabolic activation and has desirable pharmacokinetic properties that were demonstrated in preclinical and early clinical studies^{10,11}. The clinical efficacy of liposomal irinotecan was later demonstrated in a phase II clinical trial and subsequently in a phase III clinical trial (NAPOLI-1) that led to its U.S. Food and Drug Administration approval^{5,12}. The final overall survival analysis from NAPOLI-1 showed that the survival advantage for liposomal irinotecan plus 5FU–LV compared with 5FU–LV alone was maintained from the initial NAPOLI-1 analysis (median: 6.2 months vs. 4.2 months)¹³. In the final overall analysis of the NAPOLI-1 clinical trial, a response to liposomal irinotecan of 51 weeks or longer was experienced by approximately 12% of patients¹³. The estimated 1-year overall survival rates were 26% for liposomal irinotecan plus 5FU–LV compared with 16% for 5FU–LV. No patients in the NAPOLI-1 trial who survived long-term (≥ 1 year) had irinotecan-refractory disease before receiving liposomal irinotecan¹³.

A single-institution study reported that, compared with patients who had previously progressed on irinotecan-based chemotherapy, patients who were irinotecan-naïve experienced significantly longer progression-free survival (4.8 months vs. 2.2 months, $p = 0.02$) and overall survival (7.7 months vs. 3.9 months, $p = 0.002$)¹⁴. The study further reported that baseline characteristics associated with long-term survival greater than 1 year in the liposomal irinotecan plus 5FU–LV arm of NAPOLI-1 were a Karnofsky performance status score of 90 or greater, age 65 years or less, serum CA19-9 less than 59 U/mL, a neutrophil-to-lymphocyte ratio of 5 or less, and no liver metastasis¹³. More recently, the U.S. National Comprehensive Cancer Network guidelines recommended liposomal irinotecan plus 5FU–LV for patients who had received prior fluoropyrimidine-based therapy if no prior irinotecan therapy had been given².

The patient described in the present report experienced a prolonged (51-week) response to liposomal irinotecan plus 5FU–LV despite prior disease progression on irinotecan as part of FOLFIRINOX. Moreover, the patient did not have most of the baseline characteristics that were associated with long-term survival in the final overall analysis of the NAPOLI-1 clinical trial¹³. Before starting his treatment with liposomal irinotecan plus 5FU–LV, his Karnofsky performance status score was 70, his serum CA19-9 was high, his neutrophil-to-lymphocyte ratio was greater than 5 (5.59), and he had liver metastasis. Notably, he was relatively young (47 years of age), and he had received full-dose treatment at regular intervals (every 2 weeks) before disease progression was observed. The genomic profile of this patient's tumour before and after treatment with liposomal irinotecan had some confounding differences,

and it was therefore not possible to highlight meaningful molecular changes that might provide a basis for the patient's prolonged response to liposomal irinotecan.

SUMMARY

A prolonged response to liposomal irinotecan plus 5FU–LV in patients with metastatic PDAC has been described in the literature^{13,14}. Factors that are usually associated with better outcomes with that combination in patients with metastatic PDAC are no prior progression on irinotecan, Karnofsky performance status score of 90 or greater, age 65 years or less, serum CA19-9 less than 59 U/mL, a neutrophil-to-lymphocyte ratio of 5 or less, and no liver metastasis. Our patient with stage IV cancer of pancreas or bile duct experienced a prolonged (51-week) response despite prior disease progression on irinotecan and lack of any of the baseline characteristics that had previously been associated with long-term survival, except for younger age.

This case report demonstrates that prolonged response to liposomal irinotecan plus 5FU–LV has been experienced in a patient with irinotecan-refractory stage IV cancer of pancreas or bile duct. Most factors reportedly associated with better outcomes, apart from a young age, were not present in our patient. Two separate genomic profiles of the tumour had confounding differences, and it was not possible to identify a predictive molecular biomarker. Given our experience with this patient, using liposomal irinotecan plus 5FU–LV to treat patients with irinotecan-refractory metastatic PDAC is not unreasonable. Identifying predictive markers for response is an unmet need.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare the following interests: AS is an employee of Genesis Research, which receives research funding from Ipsen, the manufacturer of liposomal irinotecan (Onivyde). TP, MK, OAR have no conflicts of interest to disclose.

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