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Maintenance Treatment of Metastatic Pancreatic and Bile Duct Cancers with S-1 has Provided Prolonged Oncologic Control and Quality of Life: Case Series

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Abstract

This case series covers three patients receiving S-1 maintenance therapy after resection and adjuvant chemotherapy for either metastatic pancreatic cancer (n = 2) or bile duct cancer (n = 1). In contrast to a standard S-1 regimen involving periodic two-week pauses, patients were administered with low-dose S-1 for 5 days every week without pause. All patients showed long-term remission for around three years or more. Furthermore, patients displayed notable quality of life despite continuous dosing. Therefore, in selected cases, S-1 may provide effective long-term oncologic maintenance without severe detriments to patient lifestyle.

Keywords: Case report; Oncology; Maintenance therapy; Metastatic pancreatic cancer; Bile duct cancer; S-1

Introduction

S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan) is an effective treatment for pancreatic cancer [1,2] and bile duct cancer [3] as either first-line therapy or as a neoadjuvant/adjuvant to resection. The drug is a combination of tegafur (metabolized to 5-FU), gimeracil and oteracil that is used for disease control because it can generate high levels of 5-FU with minimal adverse events [1–7]. S-1 is believed to promote better quality of life (QOL) compared to alternative agents due to its formulation as a pill and its well-tolerated toxicity profile (i.e. it is not infused through IV and is non-detrimental to everyday life) [4,5]. However, studies of S-1 in a maintenance role typically have a limited duration (e.g. <12 months) and rigorous evidence for the QOL benefits of S-1 is uncommon.

This case series report covers three patients receiving S-1 maintenance therapy after resection and adjuvant chemotherapy, within a period from 2016 until 2022. Two of the patients had metastatic pancreatic cancer, and one had bile duct cancer. The reports follow CARE guidelines for the presentation of case studies [8] and all patients provided their informed consent to publish. The cases demonstrate that long-term remission (>2–4 years) with good QOL can be achieved using S-1 as continuous maintenance therapy.

Case Presentation

Case 1: 64–69-Year-Old Male with Metastatic Pancreatic Cancer.

In June 2017, a 64-year-old male presented to a GP with obstructive jaundice and elevated carbohydrate antigen (Ca19.9 = 44.7 U/mL). Computed tomography (CT) scan detected a primary T3N1M1 tumor at the pancreatic head with a peripancreatic lymph-node metastasis. A Whipple procedure was performed on the pancreatic head in June 2017, resecting the primary tumor from the pancreas and 7 peripancreatic lymph node metastases. The surgeon also resected a small, occult M1 liver metastasis and 2 celiac lymph node metastases that were detected intraoperatively. Resection margins were clear and minimal. The patient received FOLFIRINOX every 2 weeks for 6 cycles between July and October 2017, but a CT scan detected disease progression with peritoneal metastasis. Treatment was switched to gemcitabine + albumin-bound paclitaxel from October until December 2017, but tolerance was poor. Positron emission tomography (PET)/CT scans detected disease progression with 2 new liver metastases (segments IVa, V) and tests detected erbB2 and erbB3 expression.

The patient was referred to the clinic in January 2018, and treatment was switched to gemcitabine + capecitabine for 8 cycles (ending July 2018). Magnetic resonance imaging (MRI) and PET/CT scans suggested remission of the disease by May 2018. The patient started receiving oral S-1 (50mg twice/day [BID], 5 days/week) from July 2018 as maintenance and was still continuing with this treatment at last follow-up (November 2022). Serial imaging (MRI, PET/CT) 2–4 times per year shows that the patient has remained disease free with no signs of relapse. The patient's QOL over the S-1 maintenance course has been outstanding.

Case 2: 55–60-Year-Old Female with Advanced Pancreatic Cancer.

A 55-year-old female presented to the clinic with back pain and epigastric discomfort in August 2016. Ca19.9 was elevated (5291 U/mL) and a CT scan revealed an inoperable Stage 3 tumor in the pancreatic body with extensive vascular involvement. The patient was treated with upfront chemoradiotherapy from August until October 2016. The therapeutic course followed the MD Anderson protocol of weekly low-dose gemcitabine + cisplatin, alongside radiotherapy (45/50/56/60 Gy in 30 fractions) with 1g BID capecitabine on radiotherapy days. Oral S-1 (50mg BID, 5 days/week) was then administered from October until the tumor was deemed to be operable in December 2016 (once CT imaging revealed substantial vascular downsizing and Ca19.9 measurements reduced from 7000 to 66 U/mL). The patient was admitted to hospital in December 2016 and received distal pancreatectomy in January 2017. The final pathological report was a substantially downstaged and downsized ypT1N0 focal residual adenocarcinoma (up to 1.5cm) with no lymphovascular invasion. The resection margins were clear, but the lymphatics were damaged during the surgery, and this led to chyle leakage and a post-operative stay in ICU until March 2017.

The patient returned to the clinic and presented with steadily increasing Ca19.9 (reaching 23,168 U/mL). PET/CT scans in May 2017 revealed liver metastases in segment II. The patient was administered with 8 cycles of gemcitabine + capecitabine from May until October 2017. During this course, Ca19.9 markedly decreased to 77.9 U/mL and repeated PET/CT scans showed a near-complete response for the liver metastasis. Therefore, there was no need for further resection.

The patient was placed on S-1 maintenance from November 2017 onwards. The initial regimen was 50mg S-1 BID, 5 days a week, every week. However, the dosage schedule was reduced (because of the patient's low weight and good response) to 4 days per week in April 2018 and 3 days per week in October 2018. Follow-up PET/CT scans during this course showed a complete response with no recurrence, and serial Ca19.9 measurements remained below 10 U/mL. The S-1 maintenance (50mg tablets BID, 3 days/week) was still being continued at the most recent follow-up in November 2022. Patient QOL has remained satisfactory over the maintenance course, although there has been some detriment from hand-foot syndrome.

Case 3: 71–76-Year-Old Male with Advanced Biliary Tract Cancer.

In July 2017, a 71-year-old male presented to the clinic after receiving an extended left hemihepatectomy and caudate lobectomy and excision of the common bile duct (CBD) to remove a hilar-cholangiocarcinoma. Final pathology revealed a T1N0 tumor, with positive resection margins at the CBD and around the nerves. The patient was treated in the clinic with post-operative chemoradiotherapy (45 Gy in 25 fractions + capecitabine 1g BID on radiotherapy days from August to September 2017; capecitabine only from October 2017 to March 2018).

In November 2018, PET/CT imaging detected a relapse of metastases in the right lobe and lymph nodes, and Ca19.9 had increased to 179 U/mL. Therefore, the patient was treated with gemcitabine + oxaliplatin from November 2018 until January 2019. However, the disease was deemed inoperable and further radiotherapy was not feasible because of risk to the duodenum. The patient was apprehensive about continued chemotherapy, so he was administered with maintenance S-1 (50mg tablets BID, 5 days per week) from February 2019. Ca19.9 levels decreased shortly after, and a gradual but complete response in the liver was confirmed by serial imaging.

After almost 3 years of uneventful S-1 maintenance, PET/CT scans detected progressive disease in November 2021. MRI of the liver indicated that the disease was still inoperable, and the patient began a course of gemcitabine + cisplatin in December. Although the treatment relieved significant symptoms, it was stopped after 3 cycles due to poor tolerance. In particular, PET/CT scans in January 2022 revealed adverse events of new gross ascites and profound bone marrow suppression. A decrease in platelets and its consequent repeated tapping of ascites led to discontinuation of intravenous chemotherapy. The patient was restarted on S-1 therapy (50mg tablets BID, 5 days/week) in April 2022 to achieve disease control, based on the agent’s prior effectiveness. The disease progressed in August 2022 and S-1 treatment was stopped. The patient still continued with regular monitoring, with the most recent follow-up in November 2022.

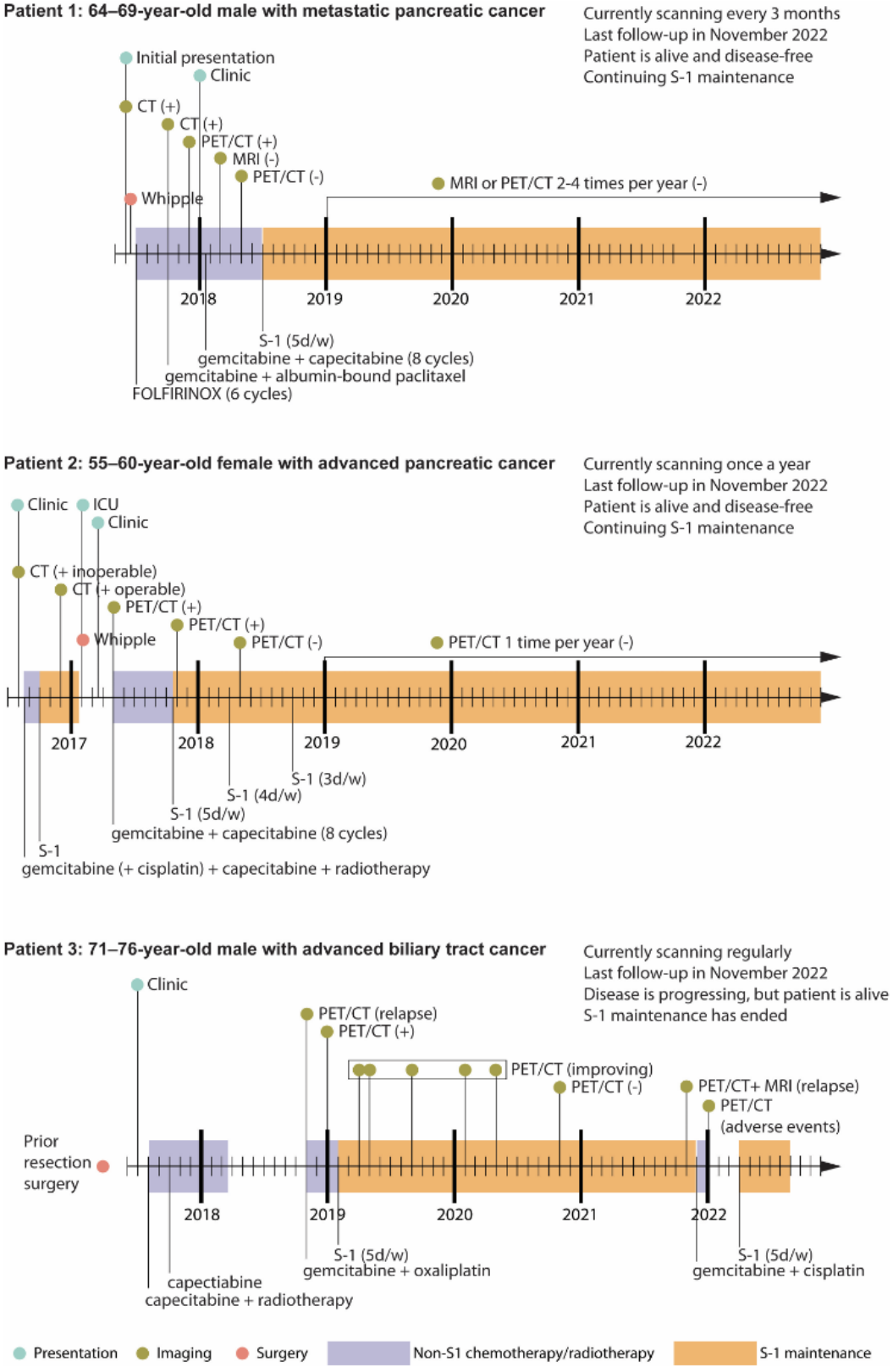

Figure 1: Timelines of events and therapeutic course for the 3 patient cases.

Discussion

According to the Surveillance, Epidemiology, and End Results (SEER) database, 5-year survival estimates for distant pancreatic cancer and localized extrahepatic bile duct cancers can be as low as 3% and 17%, respectively [9]. In my practice, the median overall survival for these diseases is expected to be about 12 months and QOL is considered poor if more than 6 months (or half the survival time) is spent in intensive treatment prior to disease progression. However, patients are expected to have better QOL during the maintenance period compared to upfront therapies.

The reported cases illustrate that maintenance therapy with S-1 can provide effective disease control with good QOL for patients with metastatic pancreatic cancer and bile duct cancer. All 3 cases accepted an upfront standard chemotherapy regimen for a defined period of 4–6 months, which was followed with low-dose but continuous S-1 maintenance. The first case strongly illustrates the apparent advantages of S-1. The patient's disease remained in remission for over three years without any notable adverse events. Importantly, the patient maintained an excellent QOL despite undertaking almost-daily chemotherapy; the patient has gained weight, managed a family business and travelled. Indeed, the administration of S-1 to this patient has little impact on his daily life. Long periods of disease control with noteworthy QOL are also observed in the other cases. The second patient has remained disease-free for over four years, whereas the third patient had three years without relapse. Furthermore, the only detriment to the second patient's health-related QOL has been a minor toxicity of hand-foot syndrome. Similarly, the third patient maintained very good QOL for three years until the recent decline in his condition. These cases are corroborated by findings from the JASPAC01 Phase III study of adjuvant S-1 chemotherapy for resected pancreatic cancer [2]. In particular, the self-reported QOL for patients receiving S-1 improved from 6 months onwards, whereas it remained stagnant for 24 months in patients using gemcitabine.

The key to the success of S-1 in these cases may stem from the alterations to its administration. Firstly, S-1 was dosed at a static 50mg BID rather than by body surface area as trialled (approx. 40mg/m^2 = 40–75mg/body) [2]. Secondly, S-1 was administered in a continuous mode (every week) rather than 4 weeks on and 2 weeks off (case 2 shows how administration can be tapered while maintaining a continuous course). This treatment regime may have altered the natural biology of the tumor, and therefore the tempo of the disease. The advantages of non-stop administration may stem from the similarity between the pharmacokinetics of orally administered S-1 and continuously infused fluorouracil [10–12], to which Uesaka et al. [2] speculate that continuous dosing of S-1 may be advantageous for exposing target cancer cells to the drug. These authors also highlight the good tolerance for S-1 after pancreatic resection, allowing it to be administered at higher dose-intensity than gemcitabine.

A continuous schedule may only be possible when patients are in relatively good physical condition before starting treatment. For example, the initial adjuvant treatments used by these patients are recognized to be relatively low in toxicity and as having few adverse side effects. Thus, these patients were not debilitated by the burdens of a prior treatment course. Other aspects of patient selection may also be important, as reports have suggested differences in S-1 pharmacokinetics and pharmacodynamics between patients from Europe, North America and East Asia [13]. In particular, S-1 appears to be better tolerated by East Asians, and consequently, such patients may better tolerate continuous doses [2].

Conclusion

S-1 maintenance therapy appears to provide long-term disease control with relatively good QOL considering the burdens of extended chemotherapy. The potential to achieve these outcomes may be related to a low-dose but continuous administration schedule, which differs from standard treatment that contains periodic pauses. However, patient selection may be an important consideration, especially when adjusting dosages and schedules from recommendations. In particular, the physical toll of preceding treatments and the pharmacological profile of patients may be worthy of attention.

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