

Efficacy of a Single-Agent Ts1 (Tegafur, Gimeracil, and Oteracil) in Recurrent Gastric Cancer after Progression from Previous Oxaliplatin, Irinotecan, and Anti-Her2 Targeted Therapy: A Case Report

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Background: Gastric cancer ranks fourth globally in cancer-related deaths, with advanced cases having a median survival of less than 12 months. Timely surgery improves survival for localized cancer, but advanced and recurring cases have low survival rates. Treatment options include 5-fluorouracil (5-FU), but TS-1, a modified form of 5-FU, shows promise. Two Japanese trials found TS-1 effective in advanced gastric cancer, with response rates of 44% and 49%, and survival periods of 207 and 250 days. TS-1 has fewer adverse effects than 5-FU. This case report demonstrates TS1's efficacy as a second-line treatment for recurrent gastric cancer post-previous therapies.

Methods: The case involves a 44-year-old Filipino woman with a 2-month history of upper GI symptoms.

Results: This case initially presented with symptoms of easy fatigability, epigastric pain, and anemia. Gastrosocopy revealed gastric adenocarcinoma, leading to radical subtotal gastrectomy and adjuvant chemotherapy with Epirubicin, oxaliplatin, and capecitabine. She achieved a complete response for nine months until a left pelvoabdominal mass was discovered and surgically removed, revealing recurrent metastatic adenocarcinoma. Treatment shifted to docetaxel, irinotecan, and Trastuzumab due to HER2neu positivity, followed by maintenance therapy with Trastuzumab plus capecitabine. In December 2022, the patient experienced epigastric pain, prompting imaging revealing a stomach mass. Despite local therapy with radiation, gastrointestinal metastasis occurred, requiring TS1 as second-line treatment. The patient remained stable for nine months until presenting with jaundice in December 2023. Imaging revealed progressive disease in the stomach, omentum, and pancreas, leading to obstructive jaundice managed with biliary drainage. However, she developed severe pneumonia, intraabdominal infection, acute kidney injury, and electrolyte imbalances, ultimately leading to her demise.

Conclusion: The utilization of TS1 as a second-line treatment for gastric cancer can be effective and shows promising results prolonging patients' progression free survival and overall survival, it underscores ongoing efforts to tackle refractory cases, emphasizing the imperative for continuous research and innovation in the field.

Introduction

Gastric cancer currently ranks as the fourth most common cause of cancer-related fatalities globally. In cases diagnosed at an advanced stage, the median survival rate is typically less than 12 months [1]. Timely detection combined with curative surgery can improve the survival prospects for localized gastric cancer [2]. However, survival rates for extensively progressed and recurring

gastric cancers persist at notably low levels. A range of methods have been attempted for these advanced and recurring cases, among them the use of 5-fluorouracil (5-FU). TS-1 is formulated through biochemical modification of 5-FU, containing tegafur, gimeracil, and oteracil potassium in a molar ratio of 1:0.4:1. [3]. Two notable phase II trials conducted in Japan examined the effectiveness of titanium silicate (TS)-1 in treating advanced gastric cancer. The results revealed response rates of 44% and 49%, progression-free survival times of 135 and 158 days, and overall survival periods of 207 and 250 days, respectively [4, 5]. TS-1 has an increased anti-tumor effect and fewer adverse reactions compared to those of 5-FU [6]. In this case report, we present the efficacy of a single agent TS1 as a second-line metastatic treatment in recurrent gastric cancer even after progression from previous oxaliplatin, irinotecan, and anti-her2 targeted therapy.

Case Presentation

We are presented with a 44-year-old Filipino female, non-hypertensive, non-diabetic with good ECOG status with a 2-month history of easy fatigability, epigastric pain not relieved with antacids, and anemia. Further, workup with gastroscopy showed necrotic mass involving the lower body, lesser curvature, and mid-body of the stomach, siewert type III, histopathology confirmed gastric adenocarcinoma with negative metastasis on full metastatic workup. She underwent radical subtotal gastrectomy, gastrojejunostomy, and jejunojejunostomy with intraoperative findings of gastric wall thickening at the greater curvature from the mid-body to the prepyloric area, there were enlarged perigastric lymph nodes and normal gastric fundus, pancreas, spleen, and mid-transverse colon. Final histopathology showed adenocarcinoma, a poorly differentiated, diffuse type with signet ring-cell features, the tumor involves the muscularis propria, and subserosal connective tissue and invades the visceral peritoneum with a tumor size of 16.5 cm, there was a lymphovascular invasion and perineural invasion present, with negative margins and all twenty-nine (29) perigastric lymph nodes were negative for metastasis. She underwent adjuvant systemic treatment with Fluoropyrimidine-based chemotherapy, an anthracycline, and a platinum agent. She completed 6 cycles of Epirubicin (50mg/m²), oxaliplatin (130mg/m²), and capecitabine (1250mg/m²) orally for 14 days on a 21-day cycle. She had a complete response with no evidence of disease for 9 months of surveillance. Last June 2021, on surveillance imaging there was noted 7x8cm left pelvoabdominal mass seen in which the patient was subjected to surgical removal. She underwent total abdominal hysterectomy with bilateral salpingo- oophorectomy, with intraoperative adhesiolysis, bowel inspection, and prophylactic appendectomy. Intraoperative findings showed that the left ovary was enlarged to 7 x 8 x 7 cm mass multiloculated, primarily solid in consistency; inadvertently ruptured one of the locules exuding brownish fluid, the right ovary measuring 3 x1.5 x 2 cm was normal, bilateral fallopian tubes were grossly normal, the uterus measuring 6 x 4 x 3 cm was grossly normal with smooth serosal surface and the appendix was grossly normal. There was a 2 x 2 cm firm well circumscribed, nodular mass in the anti-mesenteric portion of the distal sigmoid, no serosal tears, no peritoneal carcinomatosis and the liver was smooth with grossly palpable nodules.

The final histopathology report showed left ovarian poorly differentiated adenocarcinoma with signet ring cell and mucinous features, with tumor size of 10.5 cm in single widest dimension, there was no definite lymphovascular invasion identified, which were a sign of recurrence from gastric malignancy. The rest of the organs were negative for malignancy. She was MMR proficient, stable MSI, negative for PDL1 but was positive for HER2neu mutation. Thus she was started with a taxane, irinotecan, and targeted therapy with anti HER2neu, she completed 6 cycles of docetaxel (75mg/m²), irinotecan (180mg/m²), and Trastuzumab 8 mg/kg IV loading dose on Day 1 of cycle 1, then Trastuzumab 6 mg/kg IV every 21 days with few side effects such as fatigue and neutropenia she showed partial response. She continued 18 cycles of maintenance trastuzumab plus capecitabine with stable disease.

Last December 2022, she has been experiencing on-and-off epigastric pain, repeat imaging showed a lobulated, heterogeneously enhancing exophytic mass lesion seen, arising posteriorly from the

remaining greater curvature of the stomach. It measures approximately 2.5 x 2.5 x 2.8 cm. She underwent local therapy with radiation therapy, but the repeat gastroscopy showed nodular erosions on the anastomotic site of the jejunum with jejunal mass and a friable colonic mass 50 cm level from the anal verge, biopsy showed poorly differentiated carcinoma. On March 2023, she was started with single agent TS1 (tegafur, gimeracil and oteracil) 40mg/m² twice a day followed by 14 days rest as a second-line metastatic treatment for her progressive gastric cancer after previously receiving oxaliplatin, irinotecan, and trastuzumab treatment. Despite her complicated condition, she remained stable for 9 months. Last December 2023, she presented with 2 weeks history of jaundice, her latest imaging showed progressive disease locally approximately 2.7 x 2.4 x 2.8 cm (Figure. 1A), to the anterior omentum measuring 3.1 x 3.5 x 4.2 cm (Figure. 1B) and to the pancreatic head measuring approximately 4.3 x 3.3 x 4.2 cm with resultant dilatation of the biliary tree and main pancreatic duct, with abrupt cut-off, likely due to the encasement. (Figure. 1C.)

Figure 1. Whole Abdomen CT Scan. (A) Transverse section of whole abdomen CT scan showing a lobulated, heterogeneously enhancing exophytic mass arising posteriorly from the remaining greater curvature of the stomach, measuring approximately 2.7 x 2.4 x 2.8 cm (AP x T x CC). (B) Transverse section of the whole abdomen CT scan showing a large lobulated, heterogeneously enhancing mass lesion with central areas of hypodensity in the omentum. It measures approximately 3.1 x 3.5 x 4.2 cm abutting the anterior surface of the lateral segment of the left hepatic lobe and infiltrating the anterior abdominal wall extending into the subcutaneous layer. (C) Sagittal section of the whole abdomen showing mass lesion at the region of the head of the pancreas measuring approximately 4.3 x 3.3 x 4.2 cm with resultant dilatation of the biliary tree and main pancreatic duct with abrupt cut-off, likely due to encasement.

she was managed as a case of obstructive jaundice, she underwent percutaneous transhepatic biliary drainage with mild improvement in her jaundice, after weeks of hospitalization, she developed severe pneumonia, intraabdominal infection, acute kidney injury, multiple electrolyte imbalances, and subsequently succumbed to her death.

Discussion

Gastric cancer persists as a significant challenge in healthcare, with more than 1 million new cases reported worldwide in 2018 alone. It ranks as the fourth most frequently diagnosed cancer among men and the seventh among women [7]. Poorly differentiated subtype has poor survival statistics and is commonly found in younger women [8]. The survival rates for gastric cancer remain low, standing at 31% in the United States and 25% globally. Several factors contribute to these dismal statistics. Diagnosis often occurs at advanced stages of the disease, resulting in poor overall outcomes characterized by metastases, significant intratumor variability, and resistance to chemotherapy [9, 10].

In the progressive or metastatic stage, initial chemotherapy typically involves a platinum-based drug, commonly oxaliplatin, combined with a cytotoxic substance like 5-fluorouracil (5FU) and sometimes incorporating Trastuzumab if there is overexpression of HER2 [11]. On the second line treatment, other treatment options are ramucirumab, paclitaxel, an immune checkpoint inhibitor if the PD-L1 is positive, or on the latest FDA approval TAS-102 shows efficacy in progressive gastric cancer [7, 12, 13]. Progress in chemotherapy protocols has consistently elevated the 5-year survival rate for gastric cancer in the United States to 31%, marking a substantial rise from the 15% survival rate recorded in the 1970s [13]. In a study involving 51 patients treated with TS1 with progressive gastric cancer, disease control rates (DCR) were 39.2% on intention- to-treat analysis and 46.5% in patients with evaluable lesions. Median overall survival (OS) was 11 months, with one-, two-, and three-year survival rates of 49.0%, 24.8%, and 19.8% respectively. Intestinal-type adenocarcinoma and good performance status were associated with longer survival [6].

In conclusion, this case highlights several key points in the management of advanced gastric cancer. Firstly, despite aggressive treatment with surgery and chemotherapy recurrence and

metastasis occurred, underscoring the aggressive nature of this disease. Secondly, the utilization of targeted therapies such as Trastuzumab based on HER2neu positivity demonstrates the importance of molecular profiling in guiding treatment decisions and achieving partial response. And finally, the use of TS1 as a second-line treatment reflects the ongoing efforts to find effective therapies in refractory cases. This case illustrates the complex and challenging nature of advanced gastric cancer management, involving a multidisciplinary approach encompassing surgery, chemotherapy, targeted therapy, and palliative care. The utilization of TS1 as a second-line treatment for gastric cancer can be effective and shows promising results prolonging patients' progression free survival and overall survival it also had various advantages, such as its convenient oral form and mild adverse reactions. Nevertheless, to validate these findings, further prospective randomized controlled trials with a larger patient cohort are required.

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Conflict of Interest Statement

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