

# Neoadjuvant treatment with cisplatin and S-1 in elderly patients with oesophagogastric adenocarcinoma and locoregional disease: Two case reports and review of the literature

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**Abstract.** Perioperative platinum/fluoropyrimidine-based chemotherapy is the therapeutic standard for oesophagogastric cancer (OAC) patients with locoregional disease. The preoperative condition directly affects postoperative prognosis; thus, particularly for elderly patients, a perioperative regimen with a favourable side effect profile is highly desirable. In the palliative setting, the combination of cisplatin and S-1 (Cis/S-1) was found to be as effective as cisplatin/5-fluorouracil, but with a more favourable side effect profile. However, no data on this combination have been reported in the perioperative setting in Caucasian patients. To the best of our knowledge, this is the first report on the treatment outcome of two elderly Caucasian OAC patients with locoregional disease receiving two neoadjuvant 4-week cycles of intravenous Cis/S-1. Both patients tolerated the doublet therapy well. No treatment delay or dose reduction was required. In both cases, preoperative staging revealed a clear response and complete surgical resection could be performed without any complications.

## Introduction

Oesophagogastric adenocarcinoma (OAC), including adenocarcinoma of the gastro-oesophageal junction and stomach, is a major health concern, particularly in elderly patients (1). A recent study from the USA reported that approximately two-thirds of OACs were diagnosed at an advanced stage, with regional lymph node invasion or distant metastases (2). In cases with advanced T stage or regional lymph node involvement (T3/4 or N<sup>+</sup>), without evidence of distant metastases,

surgical resection with D2 lymph node dissection is indicated. The MAGIC trial in 2006 first demonstrated an improvement in 5-year survival from 23 to 36% in patients with resectable stage II and III OAC treated with six cycles of perioperative chemotherapy with 5-fluorouracil (5-FU), cisplatin and epirubicin (ECF regimen) compared with surgery alone, establishing perioperative cytostatic treatment as the new standard of care (3).

Since then, it has been demonstrated that epirubicin does not confer any additional benefit in terms of overall survival (OS) in patients undergoing preoperative chemotherapy for OAC (4). The European Society for Medical Oncology guidelines currently state that 'it may be reasonable to use any fluoropyrimidine-platinum doublet or triplet' (5). The treatment suggested herein, although not explicitly mentioned, includes cisplatin and S-1 (Cis/S-1).

The fluoropyrimidine S-1 contains tegafur (an inactive 5-FU prodrug) and the two enzyme inhibitors gimeracil and oteracil. These components improve the efficacy and safety of the cytostatic agent (6) namely tegafur, gimeracil, and oteracil. In Europe, S-1 has been approved in combination with cisplatin for the palliative treatment of advanced OAC. Furthermore, in Japan, S-1 monotherapy represents the standard of care in the adjuvant setting following OAC resection (7). In the FLAGS trial, including 1,053 patients with metastatic OAC, Cis/S-1 did not prolong OS, but exhibited a significantly improved safety profile compared with cisplatin/infusional 5-FU (8,9). The same favourable side effect profile of Cis/S-1 may also be expected in the perioperative setting. Cis/S-1 has been proven to be feasible and effective for the perioperative therapy of Asian OAC patients, but experience with perioperative Cis/S-1 in Caucasian OAC patients has not been reported thus far (10,11).

## Case reports

**Case 1.** A 75-year-old male patient with an Eastern Cooperative Oncology Group (ECOG) performance status score of 1 presented at the Department of Gastroenterology, Hepatology and Infectious Diseases (Otto-von-Guericke University Hospital, Magdeburg, Germany) in July 2016 with appetite loss and postprandial pain in the upper abdomen. Ambulatory

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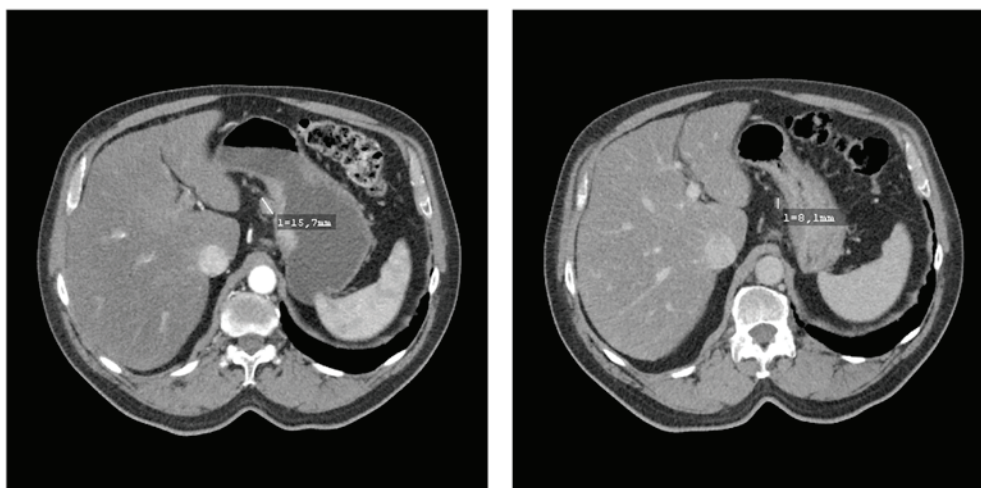


Figure 1. Case 1: Perigastric lymph node metastasis at the lesser curvature before (left) and after (right) neoadjuvant therapy on computed tomography examination.

oesophagoduodenoscopy (OGD) revealed a tumour at the gastro-oesophageal junction (Siewert type III). Repeated endoscopy with biopsy at our department confirmed the clinical suspicion. Histological examination revealed intestinal type adenocarcinoma according to the Laurén classification (12). The human epidermal growth factor receptor 2 (HER2) status was negative. There was no evidence of *Helicobacter pylori* infection. Staging computed tomography (CT) scan and endosonography revealed stage III disease (uT4uN3cM0) based on the 7th edition of the American Joint Committee on Cancer Staging Manual (2010) (13). Perioperative treatment with Cis/S-1 was initiated. Two preoperative 4-week cycles of intravenous cisplatin 75 mg/m<sup>2</sup> on day 1 and oral S-1 25 mg/m<sup>2</sup> twice daily on days 1-21 were administered. Apart from mild thrombocytopenia [grade I according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (14)] and a mild exanthema of the chest region (CTCAE v4.0 grade II), no further adverse events were observed. There was no treatment delay. The body weight remained stable during the entire course of the cytostatic treatment, and no deterioration of the ECOG score was observed. A preoperative CT scan revealed partial remission of the perigastric lymph node metastases and excluded distant metastases (Fig. 1). In early December 2016, radical gastrectomy with D2 lymph node dissection was performed. No complications occurred after surgery and the patient was discharged on the 11th postoperative day. The histopathological assessment of the resected tissue confirmed complete resection (R0) and proved partial regression (grade II according to Becker *et al*) with 20% residual tumour cells (15). After surgery, a further two cycles of cisplatin/S-1 were administered uneventfully. The last postoperative follow-up (June 2017) revealed no signs of tumour recurrence.

**Case 2.** A 71-year-old male patient in good general condition (ECOG performance status score 1) developed weakness and non-specific thoracic pain. The past medical history was remarkable for coronary heart disease, and the patient had already received two coronary stents. A recent percutaneous coronary angiography excluded significant stenoses. The laboratory tests

revealed mild iron deficiency anaemia. The next diagnostic step was an OGD with biopsies, revealing adenocarcinoma of intestinal type (according to the Laurén classification) in the gastric antrum. HER2 status and *Helicobacter pylori* serology were negative. Staging CT scan and endosonography revealed locoregional disease without distant metastases (uT3uN1cM0). Perioperative cytostatic therapy with two 4-week cycles of Cis/S-1 was administered. The side effects included dysgeusia, appetite loss and mild recurring episodes of vomiting (CTCAE v4.0 grade II), which were successfully controlled with antiemetics. During the treatment, a weight loss of 5 kg (CTCAE v4.0 grade I) was observed. Therefore, dietary supplementation with high-calorie sip feed nutrition products was prescribed. In addition, a clinically non-relevant thrombocytopenia was observed (CTCAE v4.0 grade I). No treatment delay was deemed necessary. During neoadjuvant therapy, no deterioration of the ECOG score was observed. A preoperative CT scan revealed considerable shrinking of both the primary cancer and the regional lymph node metastases (partial response).

In December 2016, a minimally invasive gastrectomy with D2 lymphadenectomy was performed uneventfully. The postoperative course was uncomplicated and the patient was discharged on the 13th postoperative day. Histopathological examination revealed negative resection margins (R0). The histological tumour regression grade according to Becker *et al* was 3 (15). Between February and March 2017, two cycles of adjuvant cisplatin/S-1 were administered; however, a dose reduction was required (cisplatin 60 mg/m<sup>2</sup>, S-1 20 mg/m<sup>2</sup> twice daily) due to nausea (CTCAE v4.0 grade III). The last follow-up CT scan (July 2017) revealed no signs of tumour recurrence.

## Discussion

We herein report the first two cases of Caucasian OAC patients receiving neoadjuvant Cis/S-1. Preoperative Cis/S-1 has been already investigated in Japanese OAC patients (10,11). However, the efficacy and side effect profile of S-1 is different between Asian and Caucasian subjects due to the differences in metabolism (16). Thus, the results of those studies may

not be transferable to Caucasian patients. In both reported cases, no serious adverse events (CTCAE v4.0 grade III/IV) were observed preoperatively, and no therapy delay or dose reduction was required. Both patients were in a good preoperative condition and the staging revealed considerable tumour shrinkage. Surgery was performed without any complications, and tumour resection with negative margins (R0) was histologically confirmed in both cases.

The only chance for cure of non-metastatic OAC is complete resection. Perioperative chemotherapy improves OS in OAC patients with locoregional disease (3,5,17,18). However, as gastrectomy and particularly oesophagectomy are high-risk procedures, the patient's preoperative general condition is crucial for the success of the interdisciplinary therapy approach. This is relevant, as OAC mostly occurs in elderly patients, and chronological age is a marker for increased physical frailty.

Whether elderly OAC patients with locoregional disease should receive perioperative triplet or a doublet chemotherapy has been investigated in recent trials. In a subgroup analysis of the FLOT65+ trial [5-FU, leucovorin and oxaliplatin with (FLOT) or without (FLO) docetaxel], the FLOT group exhibited increased chemotherapy-related toxicity and deterioration of quality of life global health status scores during the first 8 weeks of treatment compared with the FLO group (19). Another randomized study, which compared the triplet epirubicin, cisplatin and capecitabine (ECX) with the doublet CX (i.e., without epirubicin), yielded comparable efficacy results for both regimens (20). It should be noted that, in that trial, no patients in the CX and 12% of the patients in the ECX arm discontinued treatment due to toxicity. In summary, due to its inferior safety profile and potential deterioration of the preoperative general condition, neoadjuvant triplet chemotherapy should be discouraged in elderly OAC patients.

Although a platinum/fluoropyrimidine doublet regimen represents the standard of care in the perioperative therapy of OAC patients with locoregional disease, it is debatable whether perioperative regimens should be cisplatin- or oxaliplatin-based. Furthermore, no studies comparing perioperative Cis/S-1 and FLO are available. However, cisplatin and oxaliplatin have been compared as first-line treatment of advanced oesophagogastric cancer (21-23). In a German study comparing FLO to infusional 5-FU plus cisplatin (FLP regimen), oxaliplatin was safer with respect to haematological and non-haematological toxicity (i.e. nausea, vomiting and renal toxicity), but was associated with a significantly higher rate of peripheral polyneuropathy (22). In a recent phase III study comparing S-1/oxaliplatin (SOX regimen) and Cis/S-1 in Japanese OAC patients, similar results were obtained with respect to the safety issues, whereas no significant difference in terms of progression-free survival (PFS) and OS were observed between the two regimens (24,25). Haematological toxicity is reversible, nausea and vomiting are preventable, whereas renal toxicity can be monitored. On the contrary, oxaliplatin-induced polyneuropathy is frequently irreversible and may even worsen after withdrawal of the drug, consistently compromising the quality of life in OAC survivors (26). In our experience, oxaliplatin-induced peripheral polyneuropathy occurs early in the adjuvant (postoperative) phase of perioperative treatment, leading to withdrawal of the drug. In view of the

long-term neurotoxic sequelae of oxaliplatin and the lack of effective treatment options for this side effect, cisplatin-based chemotherapy may be preferred in the perioperative setting.

The fluoropyrimidine S-1 has shown favourable safety and efficacy data as palliative treatment of OAC. The FLAGS trial demonstrated significant improvements of tolerability due to the treatment with Cis/S-1 compared with Cis/5-FU, whereas OS and PFS did not differ significantly (8,27). At least one treatment-related serious adverse event (CTCAE grade >II) was observed in 29.7% in the Cis/5-FU arm compared with 20.5% in the Cis/S-1 arm. Treatment-related deaths were also significantly more common in the Cis/5-FU group (4.9 vs. 2.5%). In addition to the favourable side effect profile, other positive aspects of the Cis/S1 therapy should be highlighted. Due to the 4-week cycles, only one cisplatin infusion per month is necessary. This may result in i) improved quality of life, ii) reduced frequency of visits to the oncology department, and iii) reduced disease perception. The gained time may be invested in physical exercise and other coping strategies for a further improvement of the outcome, provided the patient's compliance is ensured.

In our experience, neoadjuvant and possibly perioperative Cis/S-1 represents a feasible, effective and well-tolerated treatment option for elderly Caucasian OAC patients with locoregional disease.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from both patients.

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