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Treatment of advanced oesophagogastric cancer with FOLFOX-4 regimen followed by leucovorin/bolus and continuous infusion 5-FU as maintenance chemotherapy in patients aged ≥ 75 years with impaired performance status



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ABSTRACT

Objectives: To evaluate the efficacy and safety of FOLFOX-4 combination chemotherapy, followed by leucovorin (LV)/bolus and continuous infusion 5-fluorouracil (5-FU) as maintenance chemotherapy in elderly (≥ 75 years) patients with advanced oesophagogastric cancer with impaired performance status (PS).

Materials and Methods: Patients with a PS score > 1 were included in this study. PS evaluations were performed by a geriatrician and two medical oncologists. FOLFOX-4 consisted of oxaliplatin concurrently with LV/bolus and continuous infusion 5-FU every 2 weeks. After a maximum of six FOLFOX-4 cycles, patients with no evidence of disease progression received maintenance treatment with LV/bolus and continuous infusion 5-FU every 2 weeks until disease progression or unacceptable toxicity.

Results: Thirty-eight patients were enrolled in this study. Of these, 32 (84.2%) patients had a PS score of 2 and six (15.7%) patients had a PS score of 3. After completion of FOLFOX-4, 18 (47.3%) patients achieved a partial response and 14 (36.8%) patients had stable disease. Thirty-two patients (84.2%) received maintenance chemotherapy for a median of eight cycles (range one to 26 cycles). The 6-month disease-control rate was 47.3% [95% confidence interval (CI) 30.9–64.1]. The median progression-free survival was 5.9 months (95% CI 4.7–6.8) and the median overall survival was 9.6 months (95% CI 8.1–11.7). Grade 3 neutropenia occurred in six patients (15.7%), and Grade 3 anaemia and thrombocytopenia occurred in two patients (5.2%).

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Conclusion: FOLFOX-4 followed by LV/bolus and continuous infusion 5-FU as maintenance chemotherapy seems to be an active and well-tolerated first-line treatment strategy for elderly patients with advanced oesophagogastric cancer and impaired PS.

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1. Introduction

Gastric cancer is the fifth most common malignancy, and the third leading cause of cancer mortality worldwide.¹ Although surgical resection offers the only chance of long-term cure, the majority of patients present with locally advanced or metastatic disease at diagnosis, and are candidates for systemic chemotherapy.² It has been estimated that approximately 50% of patients with advanced gastric cancer are over 70 years of age, and more than one-quarter are over 80 years of age.^{3,4} Among chemotherapy agents, the anthracyclines epirubicin or doxorubicin, cisplatin and oxaliplatin, the fluoropyrimidines 5-fluorouracil (5-FU) and capecitabine, and docetaxel are the most active and conventionally administered drugs in advanced gastric and gastroesophageal junction (GEJ) cancer.⁵ In addition, a randomized trial demonstrated that positive HER-2 patients may benefit from chemotherapy combined with the monoclonal antibody trastuzumab in terms of progression-free survival (PFS) and overall survival (OS).⁶ The substitution of oxaliplatin for cisplatin is often applied, and triple-agent regimens consisting of oxaliplatin and 5-FU combined with either epirubicin or docetaxel are effective and widely used first-line treatments for patients with advanced oesophagogastric cancer.^{7,8} The majority of patients enrolled in large randomized studies are usually less than 65–70 years of age and exhibit good performance status (PS). On the other hand, elderly patients often have concomitant comorbidities that complicate the administration of aggressive treatments; therefore, monochemotherapy or supportive care alone is often recommended for this patient population.^{9,10} However, elderly patients with good PS may benefit from double- or triple-agent chemotherapy which usually achieves better results than single-agent chemotherapy.¹¹ The double-agent combinations of oxaliplatin and LV/bolus and continuous infusion 5-FU (i.e. FOLFOX regimen) are widely used in advanced colorectal cancer,^{12,13} and have also shown good activity in patients with advanced gastric cancer with a response rate of approximately 30–50%, median PFS of 5–7 months and median OS of 8–11 months.^{3,14–18} The authors believe that elderly patients with compromised PS may benefit from double-agent induction chemotherapy followed by monochemotherapy for maintenance. ‘Stop-and-go’ or intermittent chemotherapy consisting of FOLFOX followed by LV/5-FU or capecitabine as maintenance has been used for patients with advanced colorectal cancer, and encouraging results have been described.^{19,20} As such, this study was designed in order to examine the clinical efficacy and safety of FOLFOX followed by LV/bolus and continuous infusion 5-FU in elderly (≥ 75 years) patients with advanced oesophagogastric cancer with impaired PS. To the authors’ knowledge, no clinical studies have been published regarding maintenance chemotherapy with fluoropyrimidines in advanced oesophagogastric cancer.

2. Patients and Methods

2.1. Eligibility Criteria

Patients aged ≥ 75 years with histologically proven, measurable, metastatic or non-resectable locally advanced gastric or GEJ adenocarcinoma, and an Eastern Cooperative Oncology Group (ECOG) PS score >1 were enrolled in this study. Patients who had received prior chemotherapy for advanced disease were excluded. Other eligibility criteria included life expectancy ≥ 3 months, adequate haematological parameters (absolute neutrophil count $\geq 1.5 \times 10^9/l$ and platelet count $\geq 100 \times 10^9/l$), creatinine less than 1.5 times the upper limit of the normal range, total bilirubin less than three times the upper limit of the normal range; aspartate and alanine aminotransferase less than three times the upper limit of the normal range, and absence of a second primary tumour other than non-melanoma skin cancer or in-situ cervical carcinoma. Patients with HER-2-positive tumours and patients with operable metastatic disease were excluded from the study, as were patients with severe cardiac dysfunction, chronic diarrhoea or uncontrolled sites of infection. Patients aged ≥ 75 years with a baseline ECOG PS score of 0–1 were excluded from the study, and triple-agent chemotherapy or other conventional chemotherapy regimens were recommended. A geriatric assessment was performed for all patients, and the geriatrician had the main role in the evaluation of PS, activities of daily living, individual comorbidities and cognitive functions of the study population. Evaluations were undertaken in collaboration with two oncologists for screening of patients before starting chemotherapy, every 2 weeks during FOLFOX chemotherapy, and every four chemotherapy cycles during the maintenance phase. Individual medical comorbidities and grade severity were identified using the Adult Comorbidity Evaluation 27 (ACE-27).²¹ Cognitive impairment was evaluated using the Mini-Mental State Examination (MMSE).²² This study was approved by the local ethical and scientific committee, and all patients gave their written informed consent.

2.2. Patient Evaluation

Pre-treatment evaluation, performed in the 2 weeks preceding study entry, included a detailed history and physical examination, a complete blood cell count with differential and platelet counts, whole-blood chemistry, and computed tomography (CT) scans and/or magnetic resonance imaging (MRI) of the chest and abdomen. The patients were clinically assessed every 2 weeks, and routine biochemical tests were performed. Treatment response by means of CT scan and/or MRI was evaluated every 12 weeks during treatment, or sooner if clinically indicated. Tumour response was assessed according to RECIST 1.1 criteria by local investigators.²³ Central radiology review was not performed.

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