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Clinical Trial

Clinical outcome of elderly patients with unresectable pancreatic cancer treated with gemcitabine plus S-1, S-1 alone, or gemcitabine alone: Subgroup analysis of a randomised phase III trial, GEST study.

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Abstract ***Background:*** In the GEST study of unresectable pancreatic cancer, S-1 demonstrated non-inferiority compared to gemcitabine, but gemcitabine plus S-1 (GS) did not show superiority over gemcitabine for overall survival (OS). We performed subgroup analysis of these data focused on the efficacy and safety of these regimens as a first-line treatment for elderly patients.
Methods: Elderly patients (≥70 years, n = 261) treated for unresectable pancreatic cancer (GS: n = 90, S-1: n = 85 and gemcitabine: n = 86) were analysed.
Results: No significant differences between the GS, S-1, or gemcitabine groups in OS (median: 10.2, 8.0 and 8.5 months, respectively) or objective response rates (27.6%, 25.3% and 14.3%, respectively) were noted. Grade ≥III adverse haematological events were observed more frequently in GS-treated than in S-1- or gemcitabine-treated elderly patients ($p < 0.001$ and $p = 0.016$, respectively). Four of 8 patients aged ≥80 years experienced serious adverse events.

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Conclusions: S-1 and gemcitabine are both efficacious options for treatment of elderly patients with unresectable pancreatic cancer. Conversely, first-line treatment of elderly patients with GS should only be used after careful consideration.

1. Introduction

Pancreatic cancer is one of the deadliest cancers and is seen predominantly in elderly patients, with the incidence peaking between ages 70 and 79 years [1–3]. As a result of the acceleration of population ageing in western countries, the number of elderly patients with this cancer is expected to increase in the future. Although the development of newer chemotherapeutic agents may offer survival benefit for patients with pancreatic cancer [4–7], treatment of elderly patients with pancreatic cancer is still a problematic issue. One reason for this difficulty is that various factors specific for elderly patients such as organ function, complications and comorbidity must be taken into account [8]. Balducci et al. stated that the incidence of geriatric problems increases sharply in cancer patients aged ≥70 years old [9], and the International Society of Geriatric Oncology recommends a comprehensive geriatric assessment for these patients [10,11]. Although age is an important factor that affects the prognosis of patients with pancreatic cancer [2,3,12], there are few data in the literature specific to this group of patients. One reason is that the majority of clinical trials exclude elderly patients by study design [13,14]. Moreover, some reports even suggested that elderly patients could not receive appropriate treatment just because of their age [15].

Our group previously reported the results of a randomised phase III trial (GEST study [ClinicalTrials.gov number, NCT00498225]) that compared gemcitabine, S-1, and gemcitabine plus S-1 (GS) as a front-line treatment for patients with locally advanced or metastatic pancreatic cancer [16]. In this trial, although S-1 demonstrated non-inferiority to gemcitabine in overall survival (OS) with good tolerance, GS did not show superiority over gemcitabine. A total of 834 patients were enrolled in this trial, which included 261 patients aged ≥70 years old. We, therefore, designed an unplanned subgroup analysis of these phase III data that focused on the efficacy and safety of these regimens for elderly patients (≥70 years old). The primary end-point of this subgroup analysis was comparison of OS in elderly patients treated with GS, S-1 or gemcitabine regimens. The secondary end-points were progression-free survival (PFS), objective response rate (RR), and safety analysis of these regimens in elderly patients. Furthermore, we compared the efficacy and safety of these regimens for elderly versus younger patients (<70 years old).

2. Methods

2.1. Study design

Data for this subgroup analysis were derived from the GEST study, a randomised phase III trial that investigated the non-inferiority of S-1 alone and the superiority of GS compared with gemcitabine alone for treatment of patients with unresectable pancreatic cancer. Details of the study design, inclusion/exclusion criteria and efficacy and safety results have been described previously [16]. Briefly, the primary end-point of the GEST study was OS. The secondary end-points were PFS, objective RR and safety. The GEST study was approved by the ethics committee or the institutional review board of each participating center. Written informed consent was obtained from all patients prior to study entry.

2.2. Treatment

Patients were randomly assigned for GS, S-1 or gemcitabine treatment group. Patients randomised to the gemcitabine regimen received gemcitabine intravenously at a dose of 1000 mg/m^2 over 30 min on days 1, 8 and 15 of a 28-d cycle. Patients randomised to the S-1 regimen received S-1 orally twice daily at a dose calculated according to the body surface area (BSA) (<1.25 m^2, 80 mg/d; ≥1.25 to <1.5 m^2, 100 mg/d; ≥1.5 m^2, 120 mg/d) on days 1 through 28 of a 42-d cycle. Patients randomised to the GS regimen received gemcitabine at a dose of 1000 mg/m^2 on days 1 and 8 plus S-1 orally twice daily at a dose based on the BSA (<1.25, 60 mg/d; ≥1.25 to <1.5 m^2, 80 mg/d; ≥1.5 m^2, 100 mg/d) on days 1 through 14 of a 21-d cycle.

Chemotherapy was delayed until recovery if neutrophils were $<1.5 \times 10^9$/l, platelets were $<100 \times 10^9$/l or if there was significant and persistent grade ≥II non-haematological toxicity. The prophylactic use of granulocyte-colony stimulating factor was not allowed. Patients were assessed for toxicity before each chemotherapy cycle using the National Cancer Institute Common Toxicity Criteria version 3.0.

Dose reductions and reasons for treatment delays have been previously reported [16].

2.3. Patient evaluation

Pre-treatment evaluation, which was performed within 2 weeks prior to study entry, included a detailed medical