Pegylated granulocyte colony-stimulating factor primary prophylaxis versus no prophylaxis in patients with unresectable pancreatic cancer treated with modified-FOLFIRINOX: a randomized, open-label, multicenter, phase 2 trial

Choong-kun Lee,[a,b,*,f] Ilhwan Kim,[c,f] Dong Hyun Seo,[b] Sejung Park,[b] Minjae Kim,[d] Sang Hun Lee,[a] Yong June Lee,[c] Jung Ho Kim,[e] Chang Gon Kim,[a] and Hye Jin Choi[a,**]

[a]Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea
[b]Sondang Institute for Cancer Research, Yonsei University College of Medicine, Seoul, South Korea
[c]Division of Oncology, Department of Internal Medicine, Inje University College of Medicine, Haeundae Paik Hospital, Busan, South Korea
[d]Yonsei University College of Medicine, Seoul, South Korea
[e]Division of Infectious Diseases, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea

eClinicalMedicine
2025;90: 103646
Published Online xxx
https://doi.org/10.1016/j.eclinm.2025.103646

Summary

Background FOLFIRINOX treatment for pancreatic cancer often causes severe neutropenia, leading to dose reductions and potentially fatal outcomes. Despite this, high-level evidence supporting pegylated granulocyte colony-stimulating factor (peg-GCSF) as the primary prophylaxis is lacking. This study aimed to determine whether primary prophylaxis of peg-GCSF can prevent severe neutropenia in patients with pancreatic cancer treated with modified-(m)FOLFIRINOX.

Methods This was an investigator-initiated, open-label, multi-institutional, randomized phase 2 trial in patients aged ≥19 years with treatment-naïve locally advanced or metastatic pancreatic cancer. Patients received oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, irinotecan 150 mg/m^2, and fluorouracil 2400 mg/m^2 via continuous infusion, every other week. After 1:1 randomization, peg-GCSF (pegteograstim 6 mg, GC Biopharma Corp.) was subcutaneously administered on day 4 for the initial eight cycles for the primary prophylaxis group, whereas no G-CSF was given to the control group. Crossover to administering peg-GCSF was permitted if patients in the control group developed grade 3–4 neutropenia during the initial eight cycles. Co-primary endpoints were grade 3–4 neutropenia or febrile neutropenia within the first eight cycles. Secondary endpoints included survival, relative dose intensity, patient-reported quality of life (QOL), and bone pain. This trial is registered with the CRIS (KCT0006536) and ClinicalTrials.gov (NCT06353581).

Findings Seventy-seven patients were enrolled from February 2022 to January 2024, with 38 in the peg-GCSF primary prophylaxis group and 39 in the control group. The primary endpoints were achieved, with significantly lower grade 3–4 neutropenia in the peg-GCSF group (2.6% vs. 38.5%, $P = 0.0001$) compared to the control group, and febrile neutropenia occurring only in controls (12.8%). With a median follow-up duration of 19.7 months, survival outcomes favored peg-GCSF, although not statistically significant. The adjusted mean change of global health status or QOL scores were significantly higher for the peg-GCSF primary prophylaxis group than for the control group ($P = 0.0264$), without an increase in reported bone pain. Survival, QOL, and bone pain were secondary endpoints.

Interpretation Peg-GCSF primary prophylaxis significantly reduced grade 3–4 neutropenia and febrile neutropenia in patients with locally advanced or metastatic pancreatic cancer treated with mFOLFIRINOX. Peg-GCSF primary prophylaxis also provided a numerical survival benefit with better patient-reported QOL. This study provides a rationale for peg-GCSF primary prophylaxis in patients with pancreatic cancer treated with mFOLFIRINOX.

*Corresponding author. Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea.
**Corresponding author.
E-mail addresses: cklee512@yuhs.ac (C.-k. Lee), CHOIHJ@yuhs.ac (H.J. Choi).
[f]These authors equally contributed as co-first authors.

Funding GC Biopharma Corp.; Severance Hospital Research Fund for Clinical Excellence; National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT).

Keywords: Pancreatic cancer; Pegylated granulocyte colony-stimulating factor; FOLFIRINOX; Peg-GCSF; Primary prophylaxis

Research in context

Evidence before this study

We searched PubMed for studies evaluating pegylated granulocyte colony-stimulating factor (peg-GCSF) as primary prophylaxis in patients with pancreatic cancer treated with (modified-) FOLFIRINOX, using the search terms "pancreatic cancer", "FOLFIRINOX", "granulocyte colony-stimulating factor", "peg-GCSF", and "primary prophylaxis". Articles published before January 1, 2024, were included. There was no randomized controlled trial that definitively established the role of peg-GCSF as primary prophylaxis in this setting. Only one single-arm prospective study (Sasaki et al., 2021) evaluated primary prophylactic peg-GCSF (pegfilgrastim) in metastatic pancreatic cancer, but the trial was terminated early after enrolling only 22 patients. All other studies suggesting a benefit of peg-GCSF prophylaxis in patients receiving (modified-) FOLFIRINOX were retrospective.

Added value of this study

To our knowledge, this is the first randomized study to prospectively evaluate the efficacy of peg-GCSF primary prophylaxis in reducing severe chemotherapy-induced neutropenia in patients with unresectable pancreatic cancer treated with modified-FOLFIRINOX. The study demonstrated a significant reduction in grade 3–4 neutropenia and febrile neutropenia in the peg-GCSF group compared to the control group. Importantly, prophylactic peg-GCSF use was associated with improved patient-reported quality of life without an increase in bone pain and showed a numerical trend toward improved survival.

Implications of all the available evidence

Findings from this randomized, multicenter phase 2 trial support the routine use of peg-GCSF as primary prophylaxis in patients receiving modified-FOLFIRINOX for locally advanced or metastatic pancreatic cancer. Initiating peg-GCSF from the start of treatment may facilitate safer chemotherapy delivery, improve patient quality of life, and potentially lead to better survival outcomes. Future phase 3 studies are warranted to confirm the survival benefit and further refine prophylactic strategies in this setting.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most aggressive and lethal cancers worldwide, with a 5-year survival rate of <10%.[1] Most patients are diagnosed at an advanced stage, and systemic chemotherapy serves as the primary treatment modality. Among the available regimens, 5-fluorouracil (5-FU), leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) is one of the most effective options, demonstrating superior survival benefits compared with gemcitabine-based therapies in patients with metastatic pancreatic cancer.[2] With its high response rate, FOLFIRINOX is also recommended as an initial treatment for locally advanced pancreatic cancer.[3] However, the intense cytotoxic nature of FOLFIRINOX is associated with significant treatment-related toxicities, particularly hematological complications such as neutropenia.

In the phase III PRODIGE 4/ACCORD 11 trial, 45.7% and 5.4% of pancreatic cancer patients treated with FOLFIRINOX suffered from grade 3 or more neutropenia and febrile neutropenia (FN), respectively.[2] Severe neutropenia or FN may lead to dose reductions, treatment delays, and life-threatening infections.[4–7] These complications negatively impact the quality of life (QOL) of patients and potentially reduce chemotherapeutic efficacy. To decrease the severe adverse effects and increase tolerability, many institutions currently use a modified version of FOLFIRINOX (mFOLFIRINOX) regimen, which omits 5-FU bolus and reduces the dose of irinotecan.[8] However, the incidences of severe neutropenia and FN are still comparable between FOLFIRINOX and mFOLFIRINOX.[9–12]

Granulocyte colony-stimulating factor (GCSF) is used to prevent chemotherapy-induced neutropenia. Pegylated GCSF (peg-GCSF) has a longer half-life than that of traditional GCSF, enabling a single-dose administration per chemotherapy cycle. Primary prophylaxis with GCSF has been tested in clinical trials and is effective in the reduction of incidence of severe neutropenia or FN, duration of neutropenia, length of hospitalization, and a modest reduction in all-cause mortality.[5,6] Current guidelines do not recommend primary prophylactic GCSF administration for patients with pancreatic cancer undergoing FOLFIRINOX treatment,[13] as no high-quality evidence supports its use in patients with pancreatic cancer. However, primary prophylactic peg-GCSF is widely used for patients with pancreatic cancer treated with FOLFIRINOX or

mFOLFIRINOX.[14,15] Despite this, prospective data on the incidence and severity of peg-GCSF-induced adverse events such as bone pain and their overall impact on QOL in patients with pancreatic cancer remain scarce. Furthermore, the clinical impact of primary prophylactic peg-GCSF on dose intensity maintenance, progression-free survival (PFS), and overall survival (OS) in the mFOLFIRINOX setting is poorly understood.

We, therefore, aimed to conduct a multi-institutional, open-label, randomized phase II trial to evaluate the efficacy and safety of primary prophylactic peg-GCSF in patients with unresectable pancreatic cancer receiving first-line mFOLFIRINOX therapy. This trial assessed the incidence of grade 3–4 neutropenia, FN, and other adverse events as well as patient-reported outcomes, including QOL and peg-GCSF-induced bone pain. We also investigated the effects of peg-GCSF on survival outcomes.

Methods

Study design and patients

This was an open-label, multi-institutional, randomized phase II trial performed at two academic cancer centers in South Korea. The trial was conducted in accordance with the Declaration of Helsinki and Guidelines for Good Clinical Practice. The protocol was approved by the Institutional Review Board of each academic cancer center. All participants provided written informed consent prior to enrollment. This trial is registered with the Korean Clinical Research Information Service (CRIS; KCT0006536) and ClinicalTrials.gov (NCT06353581). The study was prospectively registered with the CRIS—a WHO-recognized primary registry—on September 3, 2021, prior to the enrollment of the first patient, while ClinicalTrials.gov registration was completed after patient enrollment began, due to procedural requirements in our institution.

Eligible patients were men and women aged ≥19 years with histologically or cytologically confirmed PDAC assessed as locally advanced or metastatic by imaging studies, including computed tomography (CT) or magnetic resonance imaging (MRI); scheduled to receive palliative first-line mFOLFIRINOX chemotherapy; with Eastern Cooperative Oncology Group performance status of 0–1; and with adequate organ function. Major exclusion criteria were: diagnosis other than PDAC, based on histology/cytology or imaging studies (e.g., neuroendocrine tumors, etc.), moderate acute or chronic medical conditions, or abnormal findings in the examination that are judged to affect the results of this study, pregnant or breastfeeding state, and active infection that is not resolved. The full inclusion and exclusion criteria are available in the online protocol (Appendix S2).

Randomization and masking

Eligible patients were randomly assigned (1:1) to the experimental group (peg-GCSF primary prophylaxis) or the control group (no prophylaxis). Randomization was performed immediately after enrollment and prior to the initiation of treatment. Randomization did not include any stratification factors. The allocation sequence was generated using a computer-based permuted block method with a fixed block size of four by an independent biostatistician who was not involved in patient enrollment or trial conduct. Patients were assigned to each group sequentially according to the randomization table. The allocated treatments were not masked from the patients or investigators.

Procedures

The study design is presented in Appendix S1 p 2. All patients were treated with mFOLFIRINOX (intravenous oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, irinotecan 150 mg/m^2 on day 1, and 5-FU 2400 mg/m^2 46-hour continuous infusion every other week). After 1:1 randomization, peg-GCSF (pegteograstim 6 mg, Neulapeg®, GC Biopharma Corp., Korea) was subcutaneously administered on day 4 (24–72 h after end of mFOLFIRINOX) for an initial eight cycles for the primary prophylaxis group, where any type of GCSF was not administered for the control group. During the first four cycles, patients in both groups visited the hospital for hematologic toxicity surveillance 7–10 days after each mFOLFIRINOX administration, as per the investigator's discretion, in order to ensure patient safety. Thereafter, follow-up visits were limited to the days of anticancer drug administration, also at the investigator's discretion. At each clinic visit during the study, patients underwent a physical examination, assessment of ECOG performance status, adverse event monitoring, review of concomitant medications, and laboratory evaluations including complete blood count, white blood cell differential, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Crossover was permitted for the control group, if grade 3–4 neutropenia or grade 3 FN occurred during the first eight cycles of mFOLFIRINOX. Crossover patients received peg-GCSF up to eight cycles of mFOLFIRINOX as a secondary prophylactic aim, regardless of starting cycle.

All patients were treated with mFOLFIRINOX until disease progression, death, or unacceptable toxicity. CT or MRI was performed within 28 days before the first treatment dose as the baseline, and tumor responses were evaluated every 8 weeks according to the RECIST version 1.1 by investigator.

Patient-reported outcomes were assessed using the European Organization for Research and Treatment of Cancer (EORTC) 30-item Quality of Life of Cancer Patients questionnaire (QLQ-C30)[16] and a bone pain questionnaire developed specifically for this trial. Enrolled patients from both groups completed the QLQ-C30 before treatment in the first cycle (baseline) and then on day 1 of every second cycle thereafter, up to cycle 8 or treatment discontinuation. The QLQ-C30

consists of 30 questions that assess global health status or QOL: five multi-item functional scales, three multi-item symptom scales, and five single-item domains. All items were scored using the third edition of the EORTC QLQ-C30 scoring manual.[17] Briefly, enrolled patients answered questions with scores ranging from 1 (not at all) to 4 (very much), except for global health status/QOL, which used a 7-point scale. The mean scores for questions contributing to the multi-item functional or symptom scales were calculated, and the score of an individual question for a single-item domain was calculated. These scores were standardized using a linear transformation with a range of 0–100. Higher scores on global health status and functional scales reflect better functioning, whereas higher scores on symptom scales and domains indicate greater symptom burden. The bone pain questionnaire included items such as the timing (days after peg-GCSF support), location, intensity (numeric rating scale), and any pain reliever used (Appendix S1 p 3). The enrolled patients from both groups completed bone pain questionnaires at baseline and after cycles 1, 2, 3, 4, 6, and 8.

Outcomes

The primary endpoints were grade 3–4 neutropenia and FN within the initial eight cycles of mFOLFIRINOX. FN was defined as neutropenia (<1000 neutrophils/μL) with a febrile event (a single oral temperature of >38.3 °C or a temperature of >38.0 °C sustained over a 1-h period).[18] Secondary endpoints included the relative dose intensity of mFOLFIRINOX, patient-reported QOL using the EORTC QLQ-C30, adverse events assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, PFS, OS, and peg-GCSF-induced bone pain assessed using the questionnaire. The exploratory endpoint included sequential changes in cytokine levels during mFOLFIRINOX treatment with peg-GCSF support; these results will be reported separately. PFS was defined as the time from treatment initiation to the date of disease progression or death of any cause. For patients without disease progression or those who did not die, the censoring date was that nearest to the last response evaluation. OS was defined as the time from treatment initiation to death from any cause. The OS censoring date was the last date of the analysis data cutoff when the participant was alive. Relative dose intensity was calculated as the ratio of the delivered dose intensity to the planned dose intensity for each agent, expressed as a percentage. As exploratory outcomes, we performed multivariable Cox proportional hazards models to identify clinically relevant independent prognostic factors for PFS and OS. We also conducted a post hoc evaluation of the mean number of hospitalization days per patient and the proportion of patients who experienced chemotherapy dose delays of more than 4 days during the treatment period in each group.

Statistical analysis

According to previous studies conducted in Korea[14] and Japan,[19] neutropenia and FN were expected to be 15% and 5%, respectively, in the primary prophylactic group and 55% and 30%, respectively, in the control group. With statistical consideration of two-sided *p*-value of 5% (alpha 0.01 for grade 3–4 neutropenia, and alpha 0.04 for FN) and a power of 80%, 78 participants (considering 10% drop-out rate) were enrolled and 1:1 randomized to primary prophylaxis and control groups. The trial was considered successful if either of the two primary endpoints was achieved. Interim analysis was not performed.

An independent t-test was used to compare the differences between the two groups when variables were normally distributed, whereas Wilcoxon rank-sum tests were performed for non-normally distributed variables. Descriptive statistics for categorical variables, such as baseline characteristics and toxicities, including primary endpoints, are presented as counts with percentages and compared using the chi-square test or Fisher's exact test. The Kaplan–Meier method was used to estimate the OS and PFS. The log-rank test was used to determine differences in survival between groups. A Cox proportional hazards model was used to assess significant prognostic factors associated with OS and PFS using hazard ratios (HRs) and 95% confidence intervals (CIs). Safety was assessed in all patients who received at least one dose of mFOLFIRINOX during the trial.

A linear mixed-effects model was used to assess changes over time in the patient group for the different domains of the EORTC-QLQ-C30 subscales and bone pain scales. For continuous subscale scores, change from baseline was used as outcome variable, whereas for bone pain, a binary outcome (bone pain reported or not) was analyzed. Treatment, visit, and the treatment-by-visit interaction term were included as fixed effects, with baseline scores included as covariates. A random intercept was included to account for between-participant differences and a compound symmetry covariance structure was selected based on model fit, as determined by likelihood ratio testing. Adjusted mean changes from baseline were reported as least squares (LS) means with 95% CIs. For patients in the control group who crossed over to receive prophylactic peg-GCSF during treatment, QOL questionnaire data collected after the crossover point were excluded from the analysis. Bone pain details were assessed using patient-reported bone pain scales by comparing the area under the curve (AUC), time to peak severity, and average peak pain scores. A clinically meaningful change in global health status on the QOL questionnaire was defined as an absolute change of ≥10 points from baseline, indicating either deterioration or improvement. Time until definitive deterioration (TUDD) in QOL was defined according to the

previously established framework,[20] as the time from random assignment to the first deterioration, considered definitive if there was no subsequent meaningful improvement or if the patient discontinued after deterioration. Between-group differences in TUDD were assessed using a Cox proportional hazards model as a post-hoc analysis.

Statistical analyses were performed using the SAS software (version 9.4; SAS Institute, Inc., Cary, NC, USA), R (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria), and GraphPad Prism (version 8; GraphPad Software, San Diego, CA, USA). There were no missing data for the study variables. Two-sided *p*-values of <0.05 were considered statistically significant.

Role of the funding source

The funders supported the peg-GCSF (pegteograstim, GC Biopharma Corp.). The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. C-kL, IK and HJC had access to the raw data.

Results

Patients

Between February 16, 2022 and January 16, 2024, 78 patients were assessed for eligibility and randomized; 39 patients were randomized to either the peg-GCSF primary prophylaxis group or control group. After excluding one patient who declined to participate, 38 patients received primary prophylactic peg-GCSF treatment (Fig. 1) during the initial eight cycles of mFOLFIRINOX treatment. The baseline demographics and disease characteristics were generally balanced between the two groups (Table 1, Appendix S1 p 8). The median age of patients was numerically higher among primary prophylaxis group with 63.5 (interquartile range [IQR], 58.3–68) compared with 61 (IQR, 54.5–68) years in the control group ($P = 0.341$). Majority of the patients were male (73.6% and 59.0%) and had metastatic disease (73.7% and 69.2%) in the peg-GCSF primary prophylaxis and control groups, respectively. The baseline neutrophil count, inflammatory markers such as CRP, and ESR were also similar between the two groups.

Primary outcomes

The primary endpoints were achieved, with significantly lower severe neutropenic events in the peg-GCSF group compared to the control group. Among the control group (n = 39), 15 patients (38.5%) experienced grade 3–4 neutropenia during the initial eight cycles of mFOLFIRINOX, whereas only one patient (2.6%) experienced grade 3–4 neutropenia in the primary prophylaxis group (n = 38), meeting the primary endpoint of the study (2.6% vs 38.5%, odds ratio = 0.043 [95% CI, 0.005–0.349], $P = 0.0001$). Among the 15 patients who experienced grade 3–4 neutropenia in the control group, five (5/39, 12.8%) experienced FN. None of the patients experienced FN in the primary prophylaxis group. Median time to event among 15 patients who experienced grade 3–4 neutropenia in control group was 55 days (95% CI, 32.7–64.4) from day one of the first cycle of mFOLFIRINOX treatment. The mean hospitalization days per patient were longer in the control group than in the primary prophylaxis group (3.3 vs 5.1 days, $P = 0.28$, Fig. 2B), and the percentage of patients with chemotherapy dose delays (>4 days) was higher in the control group than in the primary prophylaxis group (29.0 vs 48.7%, $P = 0.075$, Fig. 2C), although these differences did not reach statistical significance.

Efficacy of mFOLFIRINOX

At data cutoff (October 30, 2024), the median follow-up duration was 19.7 months (95% CI, 19.0–22.4). All patients in the prophylaxis group received the full protocol-defined dose of peg-GCSF. The relative dose intensities of 5-FU, irinotecan, and oxaliplatin until the eighth cycle were similar between the two groups (Appendix S1 p 4–9). The median PFS was numerically longer in the peg-GCSF primary prophylaxis group than for the control group (8.4 vs. 7.1 months; HR 0.69; 95% CI, 0.42–1.16; $P = 0.14$) (Fig. 3A), similar to the trend of median OS in the two groups (12.6 vs. 10.7 months; HR 0.67; 95% CI, 0.36–1.20; $P = 0.20$) (Fig. 3B). These trends were also found among subgroups of patients with metastatic (n = 55) and locally advanced (n = 22) pancreatic cancer (Appendix S1 p 5). Multivariable analysis conducted with clinically relevant factors affecting survival showed that primary prophylactic peg-GCSF usage was an independent significant factor for better PFS (HR 0.56; 95% CI, 0.32–0.94; $P = 0.027$) and was associated with a trend toward better OS (HR 0.62; 95% CI, 0.33–1.18; $P = 0.105$) (Fig. 3C and D).

Patient-reported outcomes of quality of life and bone pain

Baseline QLQ-C30 scores were generally comparable between the two groups (Appendix S1 p 10). The mean global health status and QOL scores at baseline were 62.9 (95% CI, 56.6–69.3) in the peg-GCSF primary prophylaxis group and 65.6 (95% CI, 59.3–71.9) in the control group. The adjusted mean change from baseline in global health status or QOL scores was significantly higher in the peg-GCSF primary prophylaxis group than in the control group (1.6 vs. −0.4, $P = 0.0264$) (Fig. 4A, Appendix S1 p 11). However, all other adjusted mean changes from baseline scores for multi-item functional and symptom scales, and single-item domains were similar between the two groups (Fig. 4B, Appendix S1 p 8). Among all adjusted mean

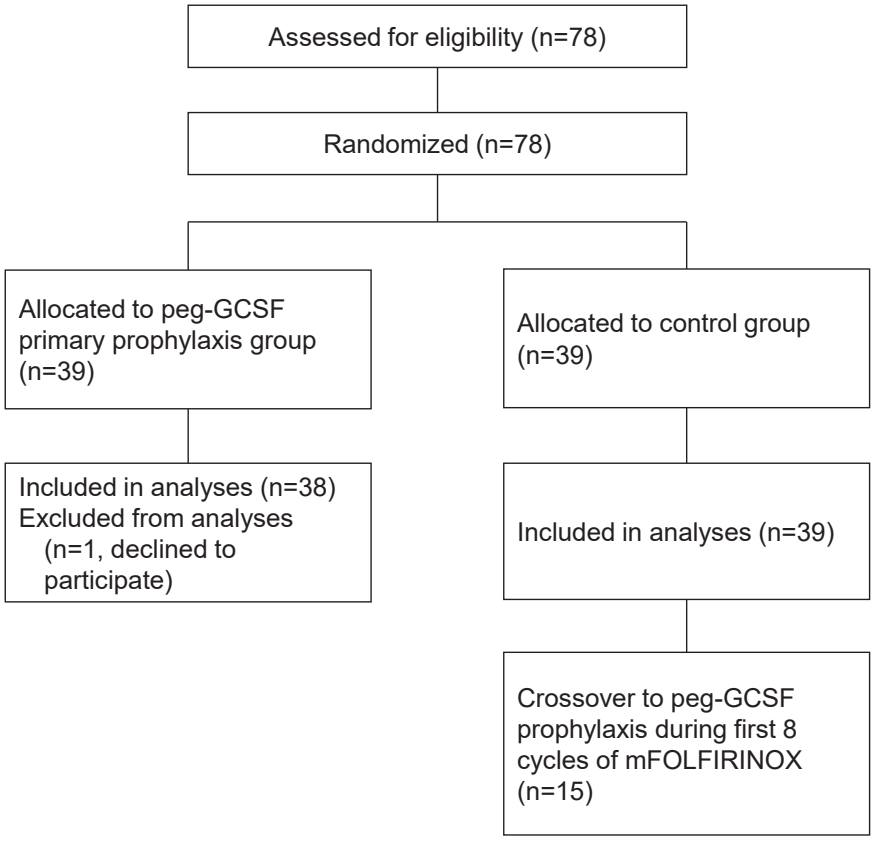

Fig. 1: Trial profile.

change from baseline scores for patient-reported outcomes, nausea and vomiting (both groups) or diarrhea (peg-GCSF group) met the predefined threshold of an absolute change of ≥10 points.[21] In the post-hoc exploratory analysis of TUDD, no statistically significant differences were observed between the two groups global health status domain (Appendix S1 p 6).

Bone pain is the most common and consistently observed adverse event associated with peg-GCSF administration.[22] To accurately assess its incidence and severity, a trial-specific bone pain questionnaire was developed and implemented (Appendix S1 p 3). The median time to the development of the most severe bone pain after peg-GCSF administration was 3 days (95% CI, 2.25–8.88). The incidence of bone pain did not differ significantly between the peg-GCSF primary prophylaxis and control groups (35.1% vs 23.1%, $P = 0.51$) (Fig. 4C). Fig. 4D shows the proportion of patients reporting bone pain at each treatment cycle, and the AUC for these proportions was similar between groups, indicating no clinically meaningful difference in bone pain incidence. The average peaks of the bone pain scale were also similar between the two groups (Appendix S1 p 7).

Adverse events other than neutropenia were similar between the two groups and primarily related to mFOLFIRINOX (Appendix S1 p 12). Nausea was more common in the peg-GCSF group (n = 18, 47.4%) than in the control group (n = 9, 23.1%), whereas increased blood bilirubin events were more frequent in the control group (n = 6, 15.4%) than in the peg-GCSF group (n = 1, 2.6%). However, most cases were of grade 1 or 2.

Discussion

Here, we report the primary results of a randomized, multi-institutional, phase II study evaluating the use of primary prophylactic peg-GCSF in patients with locally advanced or metastatic pancreatic cancer receiving first-line mFOLFIRINOX treatment. To the best of our knowledge, this is the first randomized prospective trial to assess the effect of peg-GCSF on neutropenic adverse events and the efficacy of mFOLFIRINOX, as well as patient-reported QOL and bone pain. Primary prophylaxis with peg-GCSF significantly reduced grade 3–4 neutropenia and FN events in patients receiving mFOLFIRINOX and may enhance the survival benefit of this regimen.

	Peg-GCSF (n = 38)	Control (n = 39)
Median age (years, IQR)	63.5 (58.3–68)	61 (54.5–68)
≥65	18 (47.4%)	14 (35.9%)
Sex		
Male	28 (73.6%)	23 (59.0%)
Female	10 (26.3%)	16 (41.0%)
ECOG performance status		
0	19 (50.0%)	20 (51.3%)
1	19 (50.0%)	19 (48.7%)
Disease type		
Locally advanced	10 (26.3%)	12 (30.8%)
Metastatic	28 (73.7%)	27 (69.2%)
Bone metastasis		
Yes	3 (7.9%)	2 (5.1%)
No	35 (92.1%)	37 (94.9%)
Baseline use of analgesics		
Yes	30 (78.9%)	31 (79.5%)
No	8 (21.1%)	8 (20.5%)
Prior biliary stenting		
Yes	5 (13.2%)	7 (17.9%)
No	33 (86.8%)	32 (82.1%)
CA 19-9		
Median (IQR)	417.0 (31.0–1622.5)	513.5 (25.3–2516.8)
Baseline neutrophil count (/μL)[a]		
Median (IQR)	4484 (3253–5159)	4589 (3230–6900)
Baseline C-reactive protein (mg/L)[b]		
Median (IQR)	3.1 (0.9–7.9)	3.7 (0.7–16.5)
Baseline ESR (mm/h)[c]		
Median (IQR)	23.0 (13.3–47.3)	26.0 (11.5–46.5)

ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; ESR, erythrocyte sedimentation rate. [a]Normal range for neutrophil: 1700–7000/μL. [b]Normal range for CRP: 0–8 mg/L. [c]Normal range for ESR: 0–15 mm/h.

Table 1: **Baseline patient characteristics.**

As no randomized prospective trial has previously investigated the role of GCSF or peg-GCSF support in patients with pancreatic cancer receiving FOLFIRINOX or mFOLFIRINOX, the pattern of GCSF use varies widely among clinicians and across countries. In the phase III PRODIGE 4/ACCORD 11 trial, GCSF was administered to 42.5% of patients receiving FOLFIRINOX, while 45.7% experienced grade 3–4 neutropenia.[2] Primary prophylactic GCSF has been administered in approximately 30–60% of patients with pancreatic cancer treated with FOLFIRINOX.[14,23–25] Guidelines recommend primary prophylaxis with peg-GCSF for patients at high risk (>20%) of FN.[13,26] However, the mFOLFIRINOX regimen is associated with an intermediate risk for FN, and thus, GCSF is not universally recommended as primary prophylaxis, though it may be considered for patients with high-risk clinical features. In South Korea, reimbursement for primary prophylactic peg-GCSF was recently introduced, but only for perioperative FOLFIRINOX in patients with pancreatic cancer aged ≥65 years. Contrastingly, in Japan, primary prophylactic peg-GCSF is not recommended owing to findings from a single-arm phase II trial that reported a high incidence of FN (18%) during the first cycle of FOLFIRINOX, even with primary prophylactic pegfilgrastim, leading to early trial termination.[27] In the United States, peg-GCSF is used for primary or secondary prophylaxis in patients with pancreatic cancer receiving FOLFIRINOX, depending on the institutional policies and insurance coverage. Thus, a randomized trial was warranted to evaluate the benefit of primary prophylactic peg-GCSF in patients with pancreatic cancer receiving palliative mFOLFIRINOX. We selected mFOLFIRINOX as the chemotherapy backbone given its widespread adoption in real-world practice due to improved tolerability compared to the original FOLFIRINOX regimen, especially among Asian patients.[28–31] This design choice enhances the generalizability of our findings to current standard-of-care settings where mFOLFIRINOX is routinely used.

There are limited prospective data on the risk of severe neutropenia when GCSF or peg-GCSF is not

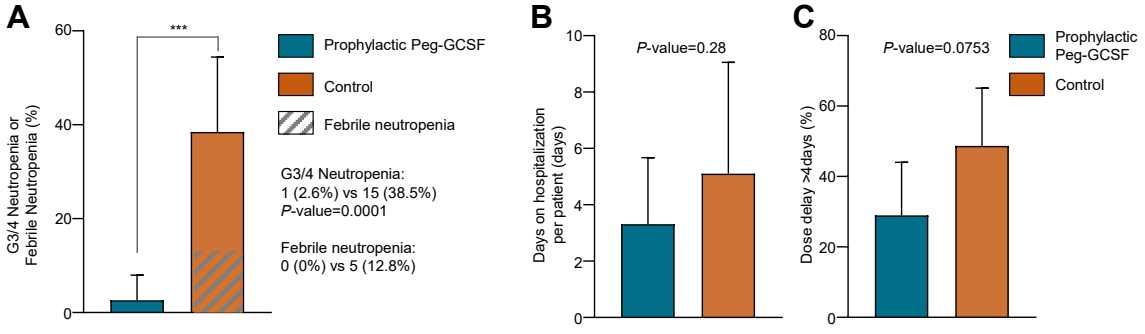

Fig. 2: **Primary outcomes and hospitalization or chemotherapy dose delays.** (A) Grade 3–4 or febrile neutropenia events for patients with pancreatic cancer with or without prophylactic peg-GCSF, during the initial eight cycles of mFOLFIRINOX. Mean hospitalization days per patient (B) and chemotherapy dose delays (C) within the eight cycles of mFOLFIRINOX with or without prophylactic peg-GCSF. Peg-GCSF, pegylated granulocyte colony-stimulating factor.

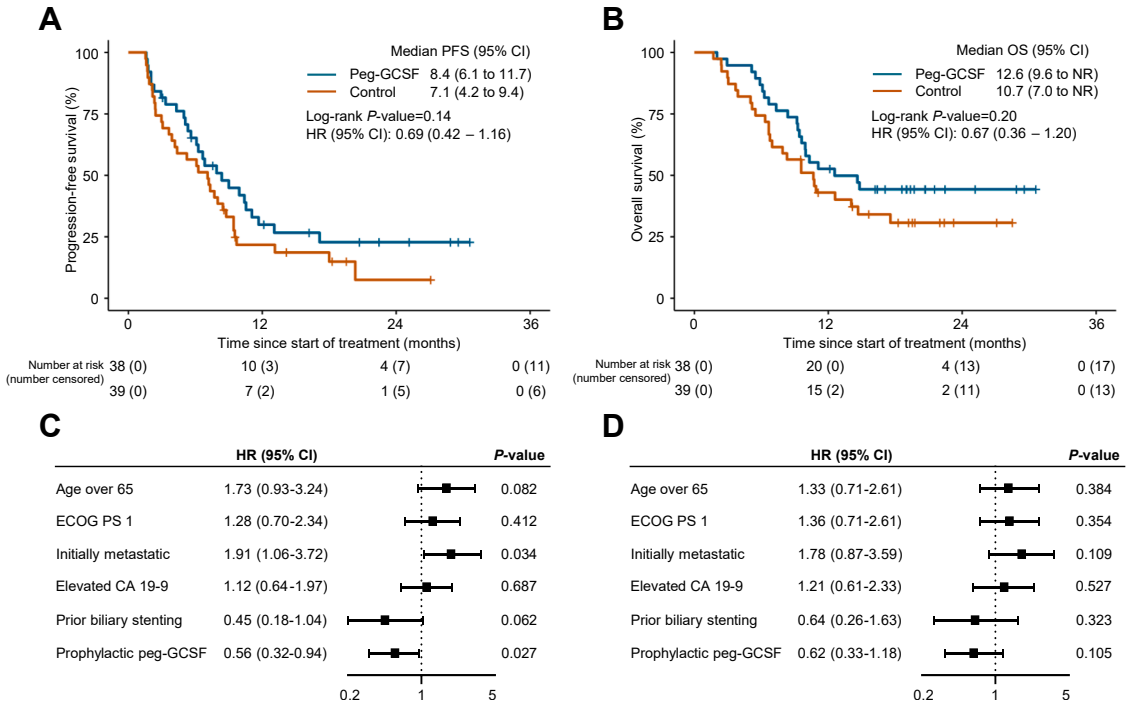

***Fig. 3:* Kaplan–Meier estimates of progression-free and overall survival.** (A) Progression-free survival (PFS) by group, (B) overall survival (OS) by group. Hazard ratios (HRs) for the peg-GCSF primary prophylaxis group versus the control group are shown. Median survival by months and 95% confidence intervals (CIs) are shown for each group. Multivariable analyses of PFS (C) or OS (D) with variables including age (≥65 vs. <65), ECOG performance status (PS) (1–2 vs. 0), disease status (initially metastatic vs. locally advanced), CA19-9 (≥37 vs. <37 U/mL), prior biliary stenting, and peg-GCSF primary prophylaxis (peg-GCSF vs. control). Peg-GCSF, pegylated granulocyte colony-stimulating factor; NR, not reached.

administered. A recent phase II trial assessing the role of perioperative mFOLFIRINOX in resectable pancreatic cancer mandated the use of pegfilgrastim and reported a 9% incidence of grade ≥3 neutropenia.[32] We used primary prophylactic pegteograstim, a peg-GCSF known to facilitate a shorter time to absolute neutrophil count recovery compared to pegfilgrastim.[33] Pegteograstim use resulted in only 2.6% of severe neutropenia and no case of FN, which was significantly lower than the 38.5% and 12.8% observed, respectively, in the absence of primary prophylaxis.

Primary prophylaxis with peg-GCSF during the initial eight cycles of mFOLFIRINOX chemotherapy led to longer PFS and OS compared to the control. Moreover, peg-GCSF prophylaxis was an independent significant factor for better PFS (HR 0.60, $P = 0.049$) and showed a trend toward better OS in multivariate analyses. There are limited reports showing the survival benefit of peg-GCSF prophylaxis.[34,35] The severe myelosuppressive effects of the mFOLFIRINOX regimen require clinicians to reduce the dosage and/or delay chemotherapy cycle administration. Therefore, maintaining the dose intensity and chemotherapy schedule is important to maximize therapeutic effects. Here, the relative dose intensities were not significantly different between the two groups. However, the percentage of patients with hospitalization or dose delays was higher in the control group than in peg-GCSF primary prophylaxis group. In addition, we prospectively collected peripheral blood samples for immune correlative analysis and plan to investigate whether G-CSF's potential immunostimulatory effects[36] contributed to the observed survival benefit.

The potential benefits of peg-GCSF must be weighed against its associated adverse effects. We utilized two patient-reported outcomes throughout the trial, to assess and compare the impact of peg-GCSF prophylaxis on QOL or bone pain symptoms. As this trial was not powered to compare QOL outcomes, changes in item scales did not differ significantly from baseline between the two groups. However, the adjusted mean change from baseline in global health status or QOL scores was significantly higher in the peg-GCSF group compared to the control group (1.6 vs. –0.4, $P = 0.0264$), indicating that patients receiving peg-GCSF experienced better overall QOL throughout the eight cycles of mFOLFIRINOX. Findings from our bone pain questionnaire indicated that the incidence of

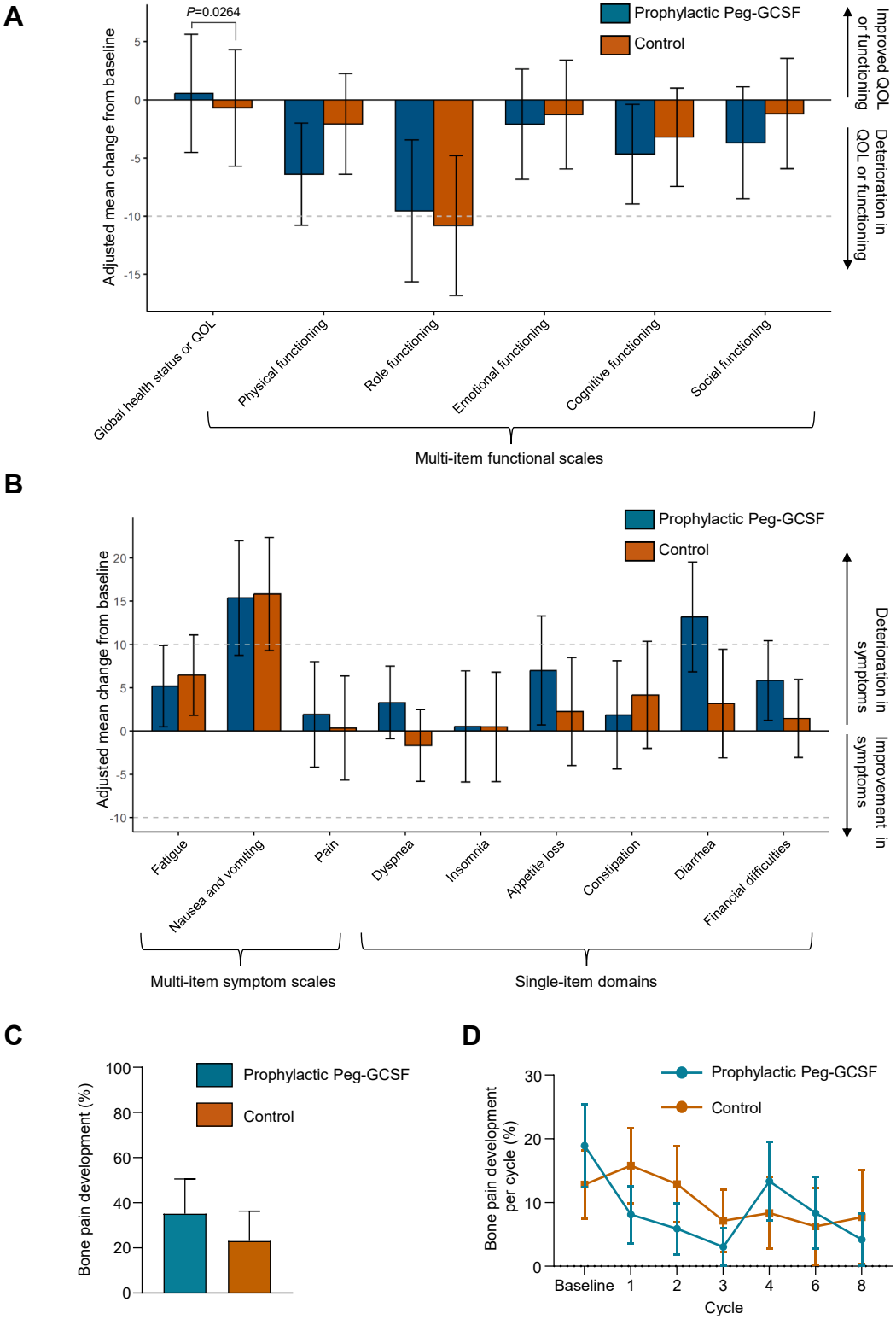

Fig. 4: **Adjusted mean changes from baseline scores for global health status or QOL and functioning (A) and symptoms (B) assessed with the QLQ-C30, and bone pain development (C, D) assessed with patient-reported outcomes.** Functioning (A) and symptoms (B) assessed with the QLQ-C30, and bone pain development (C, D) assessed with patient-reported outcomes. Dotted lines represent the pre-defined threshold of absolute change of ≥10 points. Only *P*-value <0.05 is labeled. Patients with bone pain development throughout the treatment cycles are shown in whole (C) or per cycle (D). Error bars indicate standard deviation. Peg-GCSF, pegylated granulocyte colony-stimulating factor; QOL, quality of life; QLQ-C30, 30-item Quality of Life of Cancer Patients questionnaire.

bone pain did not differ between the two groups. In addition, peg-GCSF has been shown to be cost-effective compared with daily G-CSF in various malignancies, both as primary and secondary prophylaxis for FN.[37,38] In many settings, it was not only cost-effective but also cost-saving.[39] Although no published studies to date have specifically evaluated the cost-effectiveness of peg-GCSF in pancreatic cancer patients treated with (m)FOLFIRINOX, recent analyses suggest that biosimilar peg-GCSFs are economically favorable in patient populations at intermediate-risk for FN.[40] As mFOLFIRINOX is categorized as an intermediate-risk regimen for FN in the NCCN guidelines, it is plausible that biosimilar peg-GCSF (such as pegteograstim used in this study) may provide similar economic value in this context.

This study had some limitations. First, the open-label design of this trial may have introduced bias in patient-reported outcomes such as QOL and bone pain. Second, this study was powered to compare the incidence of severe neutropenic events rather than survival or QOL outcomes. Moreover, the incidence of severe neutropenia may have been overestimated due to protocol-specified hematologic surveillance performed on days 7–10 of first four cycles. The effect of peg-GCSF prophylaxis in reducing severe neutropenia on survival and QOL improvement should be evaluated in larger trials. Third, this trial was conducted in South Korea, which may limit the generalizability of the findings. The neutropenic risk associated with mFOLFIRINOX and the response to peg-GCSF could vary among different ethnic groups.[41] Moreover, this study utilized pegteograstim as the peg-GCSF agent; efficacy and tolerability may differ from those of other peg-GCSF formulations.[42] In addition, the study population included a heterogeneous group of patients with pancreatic cancer with varying prognoses, encompassing both locally advanced and metastatic diseases. Notably, despite the higher proportion of metastatic cases in the peg-GCSF group than in the control group, survival outcomes were longer in the peg-GCSF group. An additional limitation is the absence of stratification in the randomization process. Given the eligibility criteria, patients with high tumor burden or poor performance status were likely excluded, and the short peg-GCSF exposure window may have limited the impact of disease stage on neutropenia. Although baseline characteristics were generally well balanced, future trials should incorporate stratification to reduce potential confounding.

In conclusion, this randomized phase II study of primary prophylaxis with peg-GCSF in patients with locally advanced or metastatic pancreatic cancer treated with mFOLFIRINOX met its primary endpoint, demonstrating a significant reduction in grade 3–4 neutropenia and FN compared to the control group. Peg-GCSF primary prophylaxis was associated with an improved patient-reported global health status/QOL. Our results support the use of peg-GCSF as primary prophylaxis in patients with pancreatic cancer receiving palliative mFOLFIRINOX, suggesting that it may be considered a part of the standard of care.

Contributors

Dr. Lee had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. C-kL, JHK, CGK, and HJC designed the study and developed the protocol. C-kL secured funding. C-kL, IK, SHL, YJL, CGK, and HJC participated in the recruitment of patients and collection of data. C-kL, IHK, DHS, SP, MK, and HJC analyzed the data. All authors interpreted the data. C-kL wrote the first draft of the manuscript. All authors contributed to the review and revision of the manuscript for important intellectual content and approved the final version for submission. C-kL, IK and HJC accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

The data collected for this study will not be made available to the public. Investigators interested in the deidentified participant data are encouraged to contact the corresponding author at cklee512@yuhs.ac after publication of this article for data sharing and collaboration. The protocol can be found in Appendix S2.

Declaration of interests

C-kL received honoraria from AstraZeneca, Servier, Dong-A ST, Boryung Pharmaceuticals, and Astellas; consulting fees from Eisai, Servier, Roche, and Daiichi Sankyo; and received research grants or supports from Ono Pharmaceuticals, Boryung Pharmaceuticals, GC Biopharma Corp and Lunit Inc. CGK received honoraria from Amgen, Astellas, Johnson & Johnson/Janssen, Novartis, Ono Pharmaceutical, and Pfizer; consulting fees from Astellas, AstraZeneca, Boehringer Ingelheim, Dong-A ST, Hanmi, Merck, MSD Oncology, Novartis, and Takeda. HJC received consulting fee from Beigene (outside submitted work). The other authors declare no conflicts of interest.

Acknowledgements

This investigator-initiated study was supported by GC Biopharma Corp. (South Korea), grants from the Severance Hospital Research Fund for Clinical Excellence, and grants from the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (grant number: RS-2024-00349615). We thank the patients, their families, and caregivers for participating in the study, all primary investigators, and the site personnel.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103646.

References

1 Park W, Chawla A, O'Reilly EM. Pancreatic cancer: a review. *JAMA*. 2021;326(9):851–862.
2 Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817–1825.
3 Ducreux M, Desgrippes R, Rinaldi Y, et al. PRODIGE 29-UCGI 26 (NEOPAN): a phase III randomized trial comparing chemotherapy with FOLFIRINOX or gemcitabine in locally advanced pancreatic carcinoma. *J Clin Oncol*. 2025;43(20):2255–2264.
4 Todaka A, Sasaki M, Ueno H, et al. FOLFIRINOX in pancreatic cancer: risk factors for febrile neutropenia and severe neutropenia—nationwide study analysis. *Anticancer Res*. 2023;43(9):4115–4123.
5 Lyman GH, Dale DC, Culakova E, et al. The impact of the granulocyte colony-stimulating factor on chemotherapy dose intensity and cancer survival: a systematic review and meta-analysis of randomized controlled trials. *Ann Oncol*. 2013;24(10):2475–2484.

6 Renner P, Milazzo S, Liu JP, Zwahlen M, Birkmann J, Horneber M. Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients. *Cochrane Database Syst Rev*. 2012;10(10):CD007913.
7 Sung L, Nathan PC, Alibhai SM, Tomlinson GA, Beyene J. Meta-analysis: effect of prophylactic hematopoietic colony-stimulating factors on mortality and outcomes of infection. *Ann Intern Med*. 2007;147(6):400–411.
8 Tong H, Fan Z, Liu B, Lu T. The benefits of modified FOLFIRINOX for advanced pancreatic cancer and its induced adverse events: a systematic review and meta-analysis. *Sci Rep*. 2018;8(1):8666.
9 Okusaka T, Ikeda M, Fukutomi A, et al. Phase II study of FOLFIRINOX for chemotherapy-naive Japanese patients with metastatic pancreatic cancer. *Cancer Sci*. 2014;105(10):1321–1326.
10 Irisawa A, Takeno M, Watanabe K, Takahashi H, Mitsunaga S, Ikeda M. Incidence of and risk factors for severe neutropenia during treatment with the modified FOLFIRINOX therapy in patients with advanced pancreatic cancer. *Sci Rep*. 2022;12(1):15574.
11 Li X, Ma T, Zhang Q, et al. Modified-FOLFIRINOX in metastatic pancreatic cancer: a prospective study in Chinese population. *Cancer Lett*. 2017;406:22–26.
12 Yoshida K, Iwashita T, Uemura S, et al. A multicenter prospective phase II study of first-line modified FOLFIRINOX for unresectable advanced pancreatic cancer. *Oncotarget*. 2017;8(67):111346–111355.
13 National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines®): Hematopoietic Growth Factors. Version 1.2025. National Comprehensive Cancer Network. https://www.nccn.org/guidelines/guidelines-detail?category=3&id=1493; 2025.
14 Jung JH, Shin DW, Kim J, Lee JC, Hwang JH. Primary granulocyte colony-stimulating factor prophylaxis in metastatic pancreatic cancer patients treated with FOLFIRINOX as the first-line treatment. *Cancers (Basel)*. 2020;12(11):3137.
15 Carvalho de Brito AB, Riechelmann RP, Fonseca de Jesus VH. Impact of granulocyte colony-stimulating factor (G-CSF) on the outcomes of patients with metastatic pancreatic adenocarcinoma (MPA) during first-line treatment with FOLFIRINOX: a single-center retrospective analysis. *Cancer Control*. 2023;30:10732748221149543.
16 Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365–376.
17 Aaronson NK, Ahmedzai S, Bergman B. *The EORTC QLQ-C30 Scoring Manual*. 3rd ed. Brussels: European Organisation for Research and Treatment of Cancer; 2001.
18 Health USDo, Services H. *Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0*. Bethesda, MD: National Institutes of Health National Cancer Institute; 2017.
19 Ozaka M, Ishii H, Sato T, et al. A phase II study of modified FOLFIRINOX for chemotherapy-naive patients with metastatic pancreatic cancer. *Cancer Chemother Pharmacol*. 2018;81(6):1017–1023.
20 Bonnetain F, Dahan L, Maillard E, et al. Time until definitive quality of life score deterioration as a means of longitudinal analysis for treatment trials in patients with metastatic pancreatic adenocarcinoma. *Eur J Cancer*. 2010;46(15):2753–2762.
21 Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol*. 1998;16(1):139–144.
22 Renwick W, Pettengell R, Green M. Use of filgrastim and pegfilgrastim to support delivery of chemotherapy: twenty years of clinical experience. *BioDrugs*. 2009;23(3):175–186.
23 Baldini C, Escande A, Bouche O, et al. Safety and efficacy of FOLFIRINOX in elderly patients with metastatic or locally advanced pancreatic adenocarcinoma: a retrospective analysis. *Pancreatology*. 2017;17(1):146–149.
24 Hosein PJ, Macintyre J, Kawamura C, et al. A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma. *BMC Cancer*. 2012;12:199.
25 Moorcraft SY, Khan K, Peckitt C, et al. FOLFIRINOX for locally advanced or metastatic pancreatic ductal adenocarcinoma: the Royal Marsden experience. *Clin Colorectal Cancer*. 2014;13(4):232–238.
26 Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical practice guideline update. *J Clin Oncol*. 2015;33(28):3199–3212.
27 Sasaki M, Ueno H, Mitsunaga S, et al. A phase II study of FOLFIRINOX with primary prophylactic pegfilgrastim for chemotherapy-naive Japanese patients with metastatic pancreatic cancer. *Int J Clin Oncol*. 2021;26(11):2065–2072.
28 Kang H, Jo JH, Lee HS, et al. Comparison of efficacy and safety between standard-dose and modified-dose FOLFIRINOX as a first-line treatment of pancreatic cancer. *World J Gastrointest Oncol*. 2018;10(11):421–430.
29 Cavanna L, Stroppa EM, Citterio C, et al. Modified FOLFIRINOX for unresectable locally advanced/metastatic pancreatic cancer. A real-world comparison of an attenuated with a full dose in a single center experience. *OncoTargets Ther*. 2019;12:3077–3085.
30 Uson Junior PLS, Rother ET, Maluf FC, Bugano DDG. Meta-analysis of modified FOLFIRINOX regimens for patients with metastatic pancreatic cancer. *Clin Colorectal Cancer*. 2018;17(3):187–197.
31 Jung K, Choi S, Song H, et al. Real-world dose reduction of standard and modified FOLFIRINOX in metastatic pancreatic cancer: a systematic review, evidence-mapping, and meta-analysis. *Ther Adv Med Oncol*. 2023;15:17588359231175441.
32 Cecchini M, Salem RR, Robert M, et al. Perioperative modified FOLFIRINOX for resectable pancreatic cancer: a nonrandomized controlled trial. *JAMA Oncol*. 2024;10(8):1027–1035.
33 Lee KH, Kim JY, Lee MH, et al. A randomized, multicenter, phase II/III study to determine the optimal dose and to evaluate the efficacy and safety of pegteograstim (GCPGC) on chemotherapy-induced neutropenia compared to pegfilgrastim in breast cancer patients: KCSG PC10-09. *Support Care Cancer*. 2016;24(4):1709–1717.
34 Lyman GH, Reiner M, Morrow PK, Crawford J. The effect of filgrastim or pegfilgrastim on survival outcomes of patients with cancer receiving myelosuppressive chemotherapy. *Ann Oncol*. 2015;26(7):1452–1458.
35 Miura K, Yamaguchi O, Mori K, et al. Prophylactic pegfilgrastim reduces febrile neutropenia in ramucirumab plus docetaxel after chemoimmunotherapy in advanced NSCLC: post hoc analysis from NEJ051. *Sci Rep*. 2024;14(1):3816.
36 van Eijck CWF, de Koning W, van der Sijde F, et al. A multigene circulating biomarker to predict the lack of FOLFIRINOX response after a single cycle in patients with pancreatic ductal adenocarcinoma. *Eur J Cancer*. 2023;181:119–134.
37 Gebremariam GT, Fentie AM, Beyene K, Sander B, Gebretekle GB. Cost-effectiveness of pegfilgrastim versus filgrastim for prevention of chemotherapy-induced febrile neutropenia in patients with lymphoma: a systematic review. *BMC Health Serv Res*. 2022;22(1):1600.
38 Liu Z, Doan QV, Malin J, Leonard R. The economic value of primary prophylaxis using pegfilgrastim compared with filgrastim in patients with breast cancer in the UK. *Appl Health Econ Health Policy*. 2009;7(3):193–205.
39 Eldar-Lissai A, Cosler LE, Culakova E, Lyman GH. Economic analysis of prophylactic pegfilgrastim in adult cancer patients receiving chemotherapy. *Value Health*. 2008;11(2):172–179.
40 Aapro MS, Chaplin S, Cornes P, et al. Cost-effectiveness of granulocyte colony-stimulating factors (G-CSFs) for the prevention of febrile neutropenia (FN) in patients with cancer. *Support Care Cancer*. 2023;31(10):581.
41 Lim ZL, Ho PJ, Hartman M, et al. How Asian breast cancer patients experience unequal incidence of chemotherapy side effects: a look at ethnic disparities in febrile neutropenia rates. *Cancers (Basel)*. 2023;15(14):3590.
42 Wang Y, Chen L, Liu F, et al. Efficacy and tolerability of granulocyte colony-stimulating factors in cancer patients after chemotherapy: a systematic review and Bayesian network meta-analysis. *Sci Rep*. 2019;9(1):15374.