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Impact of G-CSF Prophweylaxis on Chemotherapy Dose-Intensity, Link Between Dose-Intensity and Survival in Patients with Metastatic Pancreatic Adenocarcinoma

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Abstract

Background: In metastatic pancreatic adenocarcinoma, few data are available on the use of granulocyte-colony stimulating factor (G-CSF) prophylaxis and its impact on dose-intensity (DI), or the link between DI and progression-free survival (PFS). This study assessed the impact of G-CSF prophylaxis on the DI received by patients and the relationship between full DI and PFS according to chemotherapy regimens.

Patients and Methods: Patients from three first-line randomized phase II clinical trials were included in this retrospective cohort. G-CSF prophylaxis groups were identified and balanced according to baseline characteristics using a propensity score. Patients were classified into 2 treatment groups (FOLFIRINOX vs FOLFIRI/nab-paclitaxel (NAB)). DI was a binary variable (full/reduced). Adverse events were defined using NCI-CTCAE v4.0.

Results: Of the 498 patients, 154 (31%) were in "prophylaxis" group; 179 (36%) were treated by FOLFIRINOX and 319 (64%) by FOLFIRI/NAB. In FOLFIRINOX group, G-CSF prophylaxis was significantly associated with a higher rate of full DI (OR, 5.07; 95% CI, 1.52-16.90; $P < .01$) while in FOLFIRI/NAB group, it was significantly associated with a lower rate of full DI (OR, 0.23; 95% CI, 0.06-0.83; $P = .03$). Full DI was associated with a non-significant increase in PFS (FOLFIRINOX group: HR 0.83; 95% CI, 0.59-1.16; $P = .27$; FOLFIRI/NAB group: HR 0.84; 95% CI, 0.63-1.11; $P = .22$).

Conclusion: Granulocyte-colony stimulating factor prophylaxis was associated with a higher rate of full DI with FOLFIRINOX. Full DI was associated with a non-significant increase in PFS. These results need to be confirmed prospectively.

Key words: metastatic pancreatic adenocarcinoma; propensity score; dose-intensity; progression-free survival; granulocyte-colony stimulating factor prophylaxis.

Implications for Practice

This retrospective cohort study is one of the first to evaluate the impact of G-CSF prophylaxis on the dose-intensity of chemotherapy and not only on the incidence of adverse events such as febrile neutropenia. Its results, to be confirmed prospectively, could lead to a modification in the use of these expensive molecules in prophylaxis.

Introduction

Pancreatic adenocarcinoma (PAC) is a frequent digestive cancer with almost 500 000 new cases worldwide in 2020 and is associated with a very poor prognosis (IARC data 2020). In 1997, gemcitabine in monotherapy was established as the gold standard in the treatment of advanced PAC.[1] Starting in 2011, FOLFIRINOX[2] and gemcitabine plus nab-paclitaxel (GEMNAB)[3] have shown encouraging results, with a significant increase in overall survival (OS) in patients with metastatic pancreatic adenocarcinoma (mPAC), and became the first-line standard regimens. For each of these polychemotherapy regimens, efficacy is counterbalanced by

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a higher rate of neutropenia.[2,3] Febrile neutropenia (FN) and neutropenia <1000/mm^3 are defined as grade ≥ 3 adverse events (AEs) according to the NCI-CTCAE v4.0.[4] These complications generally lead to reduced dose intensity (DI), defined as a dose reduction and/or a cycle postponement. As reported in other cancers,[5-8] this reduction in DI could affect chemotherapy efficacy.

The prophylactic use of granulocyte-colony stimulating factor (G-CSF) reduces the occurrence and the depth of grades 3-4 neutropenia and FN.[9,10] International consensus summarizes the indications for the use of G-CSF in primary prophylaxis (PP).[11-14] The last update of the European Organisation for Research and Treatment of Cancer (EORTC)[12] recommends the prescription of G-CSF as PP for chemotherapy associated with a high probability of FN (>20%). For an average FN probability (10%-20%), prophylaxis is only recommended for patients at risk (eg risk factors: age > 65 years, advanced disease, previous FN or female). Prophylaxis is not recommended in chemotherapy with low FN probability (<10%).

Few studies have evaluated the impact of G-CSF[15-17] on chemotherapy DI in digestive oncology. Moreover, the expected rates of FN and grades 3-4 neutropenia with the most widely used chemotherapies are only known through the results of clinical trials and hospital-based series, which by definition are subject to selection bias. The FN rate in recent clinical trials[2,18] is probably underestimated because of the widespread use of G-CSF in PP or secondary prophylaxis (SP).

Using data from 3 randomized clinical trials (RCTs) (PRODIGE 35,[19] PRODIGE 37[20] and AFUGEM[21]), which tested more or less neutropenic polychemotherapy, with no recommendations in protocols regarding G-CSF use, we report here, for each regimen, practices regarding G-CSF use and the occurrence of neutropenic AEs (FN plus neutropenia grades 3-4).

We then evaluated the impact of G-CSF prophylaxis on DI and the relationship between DI and progression-free survival (PFS).

Materials and Methods

Study Population and Definition of Groups

Our study population included all patients who received at least one chemotherapy dose in one of the three mentioned RCTs, which evaluated different first-lines of chemotherapy in mPAC. The PRODIGE 35 trial evaluated FOLFIRINOX alone versus FOLFIRINOX (8 cycles) followed by simplified LV5FU2 in maintenance versus FOLFIRI3/gemcitabine alternately (every 2 months); the PRODIGE 37 trial evaluated GEMNAB/FOLFIRI3 alternately versus GEMNAB; the AFUGEM trial evaluated GEMNAB versus nab-paclitaxel + simplified LV5FU2 (detailed regimens in Supplementary Table S1). During these RCTs, prescriptions of G-CSF were prospectively registered at each cycle (type of G-CSF, date of initiation, number of injections). In the 3 RCTs, tumors were evaluated using CT-scans every 8 weeks.

Patients were classified into one of the 3 following treatment groups according to the first chemotherapy sequence (defined as the first combination of chemotherapy treatment administered to patients): FOLFIRINOX group (PRODIGE 35 arms A and B), FOLFIRI group (PRODIGE 35 arm C), and NAB group (either GEMNAB (PRODIGE 37 and AFUGEM) or LV5FU2 plus nab-paclitaxel (AFUGEM)).

Patients were also classified into 3 G-CSF prophylaxis groups. The PP group consisted of patients who received G-CSF from the first cycle and during at least 2 consecutive cycles. The SP group consisted of patients who received G-CSF from cycle n > 1 and during at least 2 consecutive cycles (also including those who received G-CSF for only 1 cycle from cycle n > 1 and who discontinued study treatment at cycle n+1). The PP and SP groups were merged into one "prophylaxis" group when assessing the impact of G-CSF prophylaxis on the DI. The "no prophylaxis" (ØP) group consisted of patients who did not receive G-CSF or were given G-CSF for curative purposes during one cycle only.

Study Objectives

The first objective of the study was to describe the use of G-CSF in PP or SP as well as rates of FN or grades 3-4 neutropenia regarding chemotherapy.

The second objective was to evaluate the impact of G-CSF prophylaxis (PP+SP) on DI received by patients treated with FOLFIRINOX or FOLFIRI/NAB. DI was considered a repeated binary variable. For one cycle, we regarded DI as full when a patient received at least 90% of all theoretical doses of each anticancer agent of the polychemotherapy regimen with no delay longer than 7 days (all delays longer than 7 days, all causes combined were considered). Otherwise, DI was considered reduced.

The last objective was to evaluate the impact of DI on PFS, defined as the time between the first day of the first chemotherapy cycle and the date of first progression (clinical or radiological) or death from any cause.

Statistical Analysis

Qualitative variables were reported with frequencies and percentages and quantitative variables with medians and ranges or interquartile ranges (IQR).

Numbers and percentages of FN and grades 3-4 neutropenia were described according to chemotherapy and G-CSF use (no G-CSF vs G-CSF). The "no G-CSF" profile consisted of ØP patients and SP patients before they received any G-CSF, and the "G-CSF" profile consisted of PP patients and SP patients after they had received G-CSF.

Propensity Score to Balance Patients' Baseline Characteristics Between the "Prophylaxis" Group and the "No Prophylaxis" Group

Some patients' baseline characteristics are known to be risk factors for FN and could influence G-CSF prophylaxis.[11,12] Because patients in the different treatment groups were not randomized according to G-CSF prophylaxis, their baseline characteristics may vary substantially between prophylaxis groups. These differences can lead to a biased evaluation of the effect of prophylaxis on the DI received. The propensity score,[22,23] defined here as the conditional probability of receiving G-CSF prophylaxis given the patients' baseline characteristics, was used to balance these covariates in the "prophylaxis" and "no prophylaxis" groups, and therefore reduce this bias. A logistic regression model was built to estimate the propensity score. The model was adjusted for the baseline characteristics. A categorical balancing score variable was then derived by grouping the estimated probabilities into 5 categories, based on the quintiles of their distribution.[23]

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Modeling the Relationship Between Prophylaxis and DI for Each Treatment Group

To analyze the impact of prophylaxis on DI, we modeled the probability of receiving a full DI according to prophylaxis through a mixed logistic regression model[24] since DI was considered a repeated binary variable (1 measurement at each cycle for each patient).

Because DI is influenced not only by FN and grades 3-4 neutropenia, which could be corrected by G-CSF prophylaxis, but also by other grades 3-4 toxicities, we included in the model: hematological AEs including anemia, thrombocytopenia, excluding neutropenia, and leukopenia; gastrointestinal AEs including diarrhea, nausea, vomiting, and mucositis; neuro-allergic AEs including paresthesia, neuropathy, allergic reaction, and palmoplantar erythrodysesthesia syndrome; deterioration in general health including anorexia; and liver AEs including increased ALT and AST and hyperbilirubinemia.

Fixed effects were estimated for prophylaxis and these severe toxicity variables. The model was adjusted for the categorical propensity score variable. The model allowed a random effect at both the patient level (to account for intra-patient correlated measurements of DI) and the chemotherapy cycle level (to account for intra-cycle correlated measurements of DI). Only DI for the first chemotherapy sequence was considered in this analysis.

Modeling the Relationship Between DI and PFS in Each Treatment Group

We fitted a Cox proportional hazard model with mixed effects[25] to explore the relationship between PFS and DI. The model allowed a chemotherapy cycle-specific random effect, and for the FOLFIRI/NAB treatment, a study-specific random effect. DI was treated as a time-varying covariate as it was evaluated at each successive chemotherapy cycle. The model was adjusted for patients' baseline characteristics. DI was considered only for the first 3 months of treatment.

Modeling Kaplan-Meier Curves Between the 3 G-CSF Prophylaxis Groups and PFS or OS

For explanatory purpose in the FOLFIRINOX group, we computed and plotted the Kaplan-Meier estimations of the PFS and OS according to previously defined prophylaxis groups (PP, SP, or ØP). The associated hazard-ratios (HRs) were calculated based on a Cox proportional hazard model.

R software version 3.6.3 (R Foundation) was used for all statistical analyses. An estimated effect associated with a *P*-value of < .05 was considered significant.

Results

Study Population and Neutropenic Events

A total of 498 patients were included in our analysis (Fig. 1). Dose reductions per drug according to each chemotherapy regimen used in the 3 RCTs are detailed in Supplementary Table S2.

The "no G-CSF" group included 417 (73.0%) patients; the "G-CSF" group included 154 (27.0%) patients (Table 1). More patients in the "no G-CSF" group than in the "G-CSF" group presented at least one FN (3.4% and 0.6%, respectively, *P* = .13). At least one grade 3 or 4 neutropenia occurred in 21.6% of patients in the "no G-CSF" group versus 18.8% of patients in the "G-CSF" group (*P* = .55).

Patients' Characteristics and Prophylaxis Groups

Patients' baseline characteristics and treatments were balanced between the "ØP", "PP", and "SP" groups except

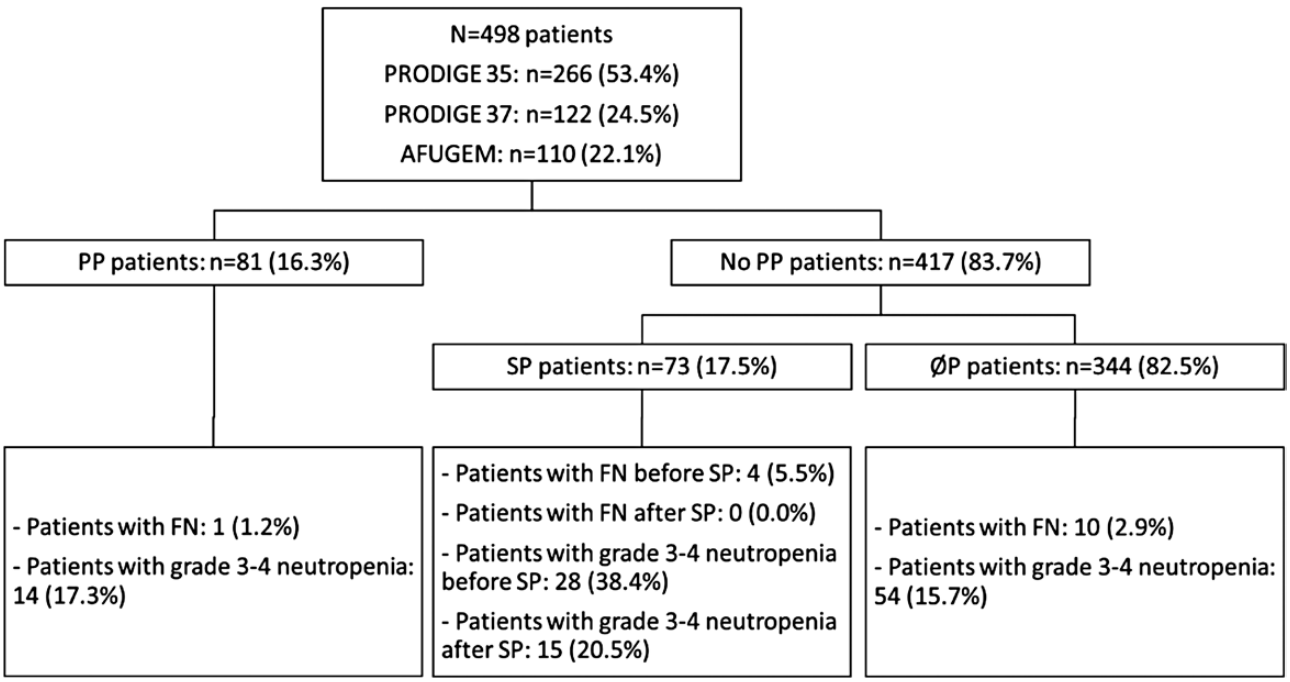

Figure 1. Study flowchart patients' classification by prophylaxis group. PP, primary prophylaxis; ØP, no prophylaxis; SP, secondary prophylaxis; FN, febrile neutropenia.

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Table 1. Rates of FN and grades 3-4 neutropenia according to "no G-CSF" and "G-CSF" groups.

	Episodes of FN/patient			Episodes of grades 3-4 neutropenia/patient			
	0	1	2	0	1	2	>2
	Percentage of patients			Percentage of patients			
No G-CSF (*N* = 417)[a]	96.6	3.4	0	78.4	19.2	1.7	0.7
FOLFIRINOX (*N* = 112)	96.4	3.6	—	70.5	27.7	1.8	—
FOLFIRI (*N* = 83)	100	—	—	85.5	12.1	2.4	—
NAB (*N* = 222)	95.5	4.5	—	79.7	17.5	1.4	1.4
G-CSF (*N* = 154)[b]	99.4	0	0.6	81.2	13.6	3.3	1.9
FOLFIRINOX (*N* = 113)	99.1	—	0.9	85.0	10.6	2.7	1.7
FOLFIRI (*N* = 11)	100	—	—	100	—	—	—
NAB (*N* = 30)	100	—	—	60.0	30.0	6.7	3.3

[a]ØP and SP patients before prophylaxis.
[b]PP patients and SP patients after prophylaxis.
FN, febrile neutropenia.

Table 2. Patients' baseline characteristics and treatments according to prophylaxis groups.

	ØP (*N* = 344)	PP (*N* = 81)	SP (*N* = 73)	PP+SP (*N* = 154)	Total (*N* = 498)
	%	%	%	%	%
Sex					
Male	59.0	58.0	53.4	55.8	58.0
Female	41.0	42.0	46.6	44.2	42.0
Treatment					
FOLFIRINOX	19.2	82.7	63.0	73.4	35.9
FOLFIRI	22.1	4.9	9.6	7.1	17.5
NAB	58.7	12.4	27.4	19.5	46.6
WHO PS					
0	39.0	45.7	34.2	40.3	39.4
1	52.3	51.8	65.8	58.4	54.2
2	8.7	2.5	0	1.3	6.4
Age					
<65 years	48.0	40.7	53.4	46.7	47.6
≥65 years	52.0	59.3	46.6	53.2	52.4
BSA					
<2 m²	86.1	88.9	87.7	88.3	86.8
≥2 m²	13.9	11.1	12.3	11.7	13.2
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
ANC, /mm³	5546 (4354-7400)	5200 (4004-6480)	5154 (3527-7200)	5177 (3798-6785)	5482 (4125-7160)
Hemoglobin, g/dL	12.7 (11.8-13.9)	13.1 (11.9-14.0)	13.3 (12.1-14.2)	13.2 (12.0-14.1)	12.9 (11.9-13.9)

ØP, no prophylaxis; PP, primary prophylaxis; SP, secondary prophylaxis; WHO PS, WHO performance status; BSA, body surface area; IQR, interquartile range; ANC, absolute neutrophils count.

for treatment, age, and absolute neutrophil count (ANC; Table 2). The proportion of patients over 65 years was higher in the "PP" group than in the "SP" or "ØP" groups. All patients had ANC > 1500/mm³ at baseline but the median ANC was higher in the "ØP" than in the "PP" and "SP" groups.

Patients' demographic and disease characteristics according to the 3 RCTs are summarized in Supplementary Table S3.

Patients treated with FOLFIRINOX more frequently received G-CSF ("PP": 37%; "SP": 26%; "ØP": 37%) than did those treated with FOLFIRI ("PP": 5%; "SP": 8%; "ØP": 87%) or NAB ("PP": 4%; "SP": 9%; "ØP": 87%; Supplementary Table S4). Moreover, regarding only patients with G-CSF prophylaxis, patients in the FOLFIRINOX group more frequently received G-CSF PP than did patients in the FOLFIRI/NAB group (59% vs 34%; $P < .01$; see Supplementary Table S5).

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Impact of G-CSF Prophylaxis on DI

All available risk factors, except albumin due to missing data, were included in the propensity score. The logistic model results used for propensity score building is presented in Supplementary Table S6. Results from the multivariate DI analysis, adjusted for the propensity score variable, are presented in Table 3.

In patients treated with FOLFIRINOX with (*N* = 113) or without (*N* = 66) G-CSF prophylaxis, G-CSF prophylaxis or the occurrence of at least one grades 3-4 gastrointestinal AE was significantly associated with a greater likelihood of receiving full DI. In contrast, in patients treated with FOLFIRI/NAB with (*N* = 41) or without (*N* = 278) G-CSF prophylaxis, G-CSF prophylaxis and a grades 3-4 deterioration in general health were associated with a lower likelihood of receiving full DI.

Impact of DI on PFS

In both groups, full DI was associated with a trend toward an increase in PFS (Table 4). In the FOLFIRINOX group, a WHO performance status equal to 1 and age below 65 years were associated with a trend toward a decrease in PFS. In the FOLFIRI/NAB group, a WHO performance status of 2 was significantly associated with a decrease in PFS.

Kaplan-Meier Curves, Prophylaxis Types, and Survival in the FOLFIRINOX Group

In the FOLFIRINOX group (*N* = 179), the median PFS was 7.85 months in the SP group, 6.43 months in the PP group and 4.00 months in the ØP group. Compared with the ØP group, the PFS hazard-ratio was 0.52 [0.35-0.76] (*P* < .01) for SP group and 0.56 [0.39-0.80] (*P* < .01) for PP group. No significant difference for SP versus PP was observed (HR = 0.92; 95% CI [0.62-1.36]; *P* = .67; Fig. 2). The same approach was used for OS, and the results are presented in Supplementary Figure S1; Kaplan-Meier curves for prophylaxis groups (PP + SP) versus no prophylaxis group (ØP) are also presented in Supplementary Figure S1.

Table 3. Estimated OR from multivariate DI analysis (full vs reduced) adjusted for the propensity score variable.

Variables		OR [95% CI]	*P*-value
FOLFIRINOX group			
G-CSF prophylaxis	Yes vs no	5.07 [1.52-16.90]	<0.01
Hematological AEs (grades 3-4)	Yes vs no	0.52 [0.08-3.37]	0.50
Gastrointestinal AEs (grades 3-4)	Yes vs no	4.72 [1.48-15.10]	0.01
Neuro-allergic AEs (grades 3-4)	Yes vs no	0.67 [0.06-6.92]	0.73
Deterioration in general health (grades 3-4)	Yes vs no	1.11 [0.29-4.18]	0.88
Liver AEs (grades 3-4)	Yes vs no	1.32 [0.15-11.76]	0.80
FOLFIRI/NAB group			
G-CSF prophylaxis	Yes vs no	0.23 [0.06-0.83]	0.03
Hematological AEs (grades 3-4)	Yes vs no	0.76 [0.19-3.04]	0.69
Gastrointestinal AEs (grades 3-4)	Yes vs no	2.32 [0.78-6.90]	0.13
Neuro-allergic AEs (grades 3-4)	Yes vs no	0.49 [0.07-3.45]	0.47
Deterioration in general health (grades 3-4)	Yes vs no	0.32 [0.12-0.87]	0.03
Liver AEs (grades 3-4)	Yes vs no	0.45 [0.15-1.39]	0.17

OR, odds-ratio; CI, confidence interval; AEs, adverse events.

Table 4. Cox proportional hazard mixed model results for PFS analysis.

Variables		HR [95% CI]	*P*-value
FOLFIRINOX group			
Dose-intensity	Full vs reduced	0.83 [0.59-1.16]	0.27
Age (year)	≥65 vs <65 years	0.74 [0.54-1.01]	0.06
WHO PS	1 vs 0	1.33 [0.98-1.81]	0.07
Sex	Male vs female	0.95 [0.69-1.30]	0.73
FOLFIRI/NAB group			
Dose-intensity	Full vs reduced	0.84 [0.63-1.11]	0.22
Age (year)	≥65 vs <65 years	0.79 [0.60-1.06]	0.11
WHO PS	1 vs 0	1.16 [0.86-1.57]	0.32
	2 vs 0	2.70 [1.61-4.51]	<0.01
Sex	Male vs female	1.07 [0.81-1.41]	0.66

HR, hazard-ratio; CI, confidence interval; WHO PS, WHO performance status.

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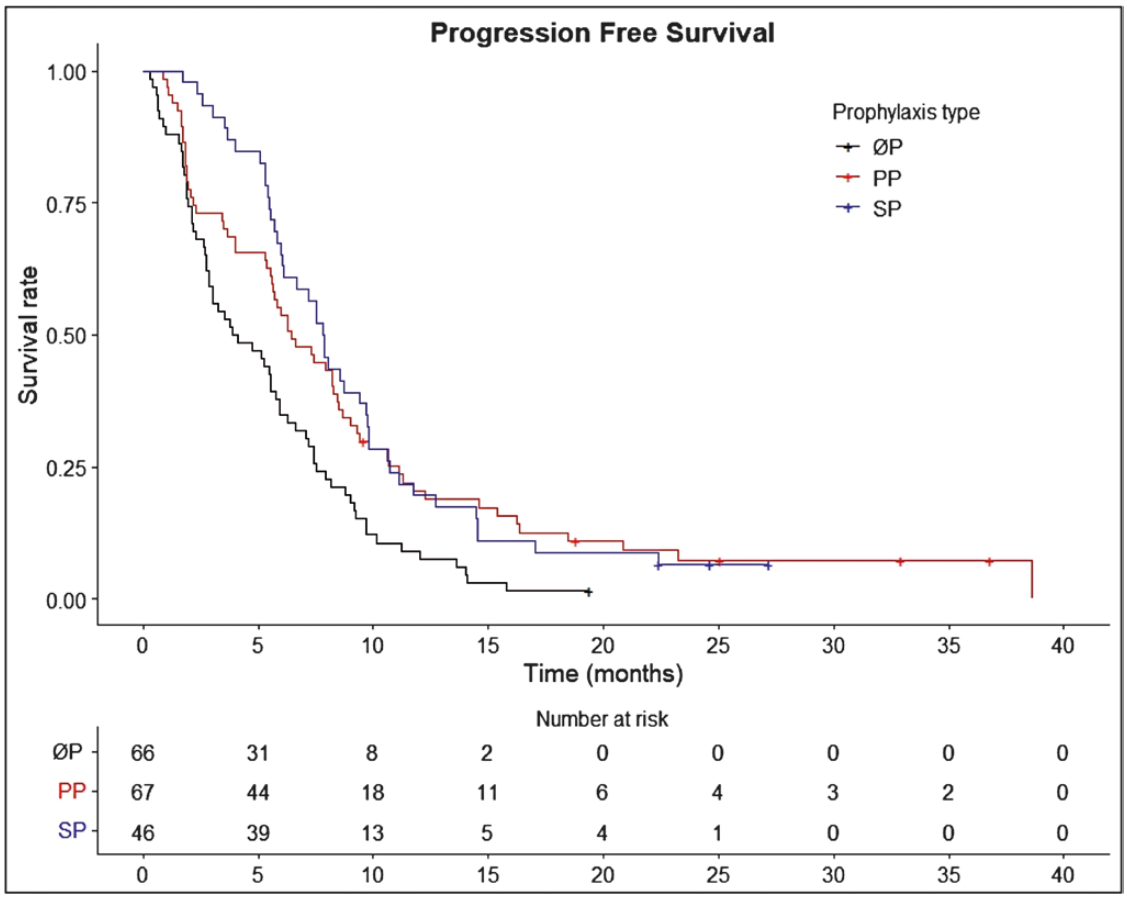

Figure 2. Kaplan-Meier estimates of PFS according to prophylaxis group. Kaplan-Meier curve for PFS. PP, primary prophylaxis; ØP, no prophylaxis; SP, secondary prophylaxis.

Discussion

In our study on patients with mPAC, G-CSF prophylaxis was associated with a higher rate of full DI in the FOLFIRINOX group. In contrast, G-CSF prophylaxis was associated with a lower rate of full DI in the FOLFIRI/NAB group. Even although the 2 treatment groups we compared were not randomized according to G-CSF prophylaxis, the propensity score allowed us to build 2 well-balanced groups for our analysis. Nevertheless, we found a non-significant association between full DI and better PFS in both groups.

Studies conducted in onco-hematology,[26] breast cancer[27] or urothelial cancer[28] have highlighted the positive impact of G-CSF on DI and/or survival. A systematic review of randomized controlled trials in patients with non-Hodgkin's malignant lymphoma treated with intensive chemotherapy showed that G-CSF PP versus no G-CSF PP was significantly associated with higher DI.[29] An observational study conducted in patients mainly with hematological malignancies (63.8%) showed that G-CSF prophylaxis (no type specified) divided by 5 in-hospital mortality from sepsis or pneumonia.[30] In a meta-analysis including results from 59 randomized G-CSF trials in non-digestive cancers,[31] G-CSF use was significantly associated with both higher DI and a reduced risk of death [RR = 0.93; 95% CI: 0.90-0.96; $P < .001$].

To the best of our knowledge, there are very few data[32,33] in digestive oncology on the impact of G-CSF on DI and/or survival. The major strength of our study is to be the first to bring original data on the use of G-CSF, to assess the relationship between G-CSF prophylaxis (all types) and DI received by patients with mPAC. This is of major interest considering the recent and widespread use of hematotoxic polychemotherapy in PAC.

Using RCT data, we showed that the use of G-CSF prophylaxis depended not only on the chemotherapy and age but also, probably, on practices in the different centers. We could not take into account a center effect because of the large number of centers, and the fact that some of them had included only 1 or 2 patients. We also observed that G-CSF prophylaxis was used outside EORTC recommendations[12] in some patients, probably with the intention to maintain a full DI.

Furthermore, recommendations on G-CSF use[11,12,34] are based on the results of studies dealing mainly with breast, lung, gynecological, urological, hematological, and colorectal cancers. The only regimen included in these recommendations for PAC is the combination of irinotecan and gemcitabine. This regimen is not very hematotoxic, and today, is no longer used. The risk of FN with other regimens is not clearly established, in particular with respect to FOLFIRINOX. In Conroy's study,[2] FOLFIRINOX was associated with 5.4% FN and 45.7% grades 3-4 neutropenia. In this study, G-CSF prescription was left to the discretion of the investigator and 42.5% of patients in the FOLFIRINOX group received G-CSF prophylaxis during the trial. It was therefore impossible to have an accurate idea of the FN rate induced by the regimen in the absence of G-CSF prophylaxis. In our cohort, the rate

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prophylaxis reached 63%, showing that G-CSF prophylaxis is widely used with FOLFIRINOX.

We found a significant relationship between G-CSF prophylaxis and a higher proportion of full DI for the FOLFIRINOX group, while G-CSF prophylaxis was associated with a lower proportion of full DI for the FOLFIRI/NAB group. The hypothesis is that, as FOLFIRINOX is expected to be hematotoxic, G-CSF prophylaxis was mainly used as a PP to decrease the occurrence of severe white blood cell toxicity and to maintain full DI. Conversely, as FOLFIRI/NAB is not expected to be hematotoxic, G-CSF was given as SP in patients with previously reduced DI. This hypothesis is based on the observed proportions of PP and SP according to the treatment group (Supplementary Table S5).

We also found a positive but non-significant relationship between PFS and full DI regardless of the chemotherapy. This exploratory analysis was carried out on robust data from a relatively small sample of patients. The small sample size may explain the absence of significant differences; however, the results seem to be interesting with regard to the optimization of patient care, in particular at a time when FOLFIRINOX is being evaluated in numerous trials as a neo-adjuvant treatment for resectable PAC or as an induction treatment for borderline/locally advanced PAC. The results of this study are in accordance with those of the meta-analysis conducted by Lyman,[31] which showed a decrease in the relative risk of all-cause mortality in patients who received G-CSF. Given the high cost of G-CSF treatments in France,[35] as well as the AEs and the impact on quality of life that these drugs can have, a prospective study evaluating the efficacy and the benefit-risk ratio of prophylaxis on dose-intensity and survival (PFS and OS) seems essential. Indeed, if the improvements in PFS and OS with G-CSF prophylaxis in hematotoxic protocols were confirmed, with a favorable benefit-risk ratio, this would be a strong argument for recommending systematic prophylaxis with hematotoxic chemotherapy.

In a completely exploratory and non-generalizable way, we plotted Kaplan-Meier curves modeling the relationship between the different types of prophylaxis as we defined them (PP, SP, and ØP) and survival (PFS or OS). Only the FOLFIRINOX group was included in this analysis because the number of patients receiving prophylaxis (PP or SP) in the FOLFIRI/NAB group was too small (see Supplementary Data 4). This analysis did not correspond to one of our objectives and is there only to illustrate a possible relationship that could exist between the 2 variables. Despite the exploratory nature of the analysis, we can see a trend toward improved survival when patients receive G-CSF prophylaxis. These curves should be interpreted with caution, and only a RCT would show the impact of prophylaxis on survival and be able to distinguish between the impact of PP and that of SP.

Our study has several limitations. First, it was a retrospective study based on clinical trial data. There is therefore a selection bias and the results cannot be extrapolated to the general population. Due to its retrospective design, some interesting data not collected at the time of the trials, such as the neutrophil-lymphocyte ratio, which has been shown to be of interest in other studies,[36,37] could not be studied. Second, the clinical trials considered for this study evaluated heterogeneous first-line chemotherapy. This required us to limit our analysis to the first chemotherapy sequence received by the patients. Finally, in order to harmonize data and to allow their inclusion in complex models, the simplification of some variables (eg such as considering DI a binary variable) made the data less informative.

Conclusion

G-CSF prophylaxis is prescribed in almost two-thirds of patients treated with FOLFIRINOX for mPAC. However, it was mainly prescribed outside recommendations, and principally to maintain a high DI. G-CSF prophylaxis in patients treated with FOLFIRINOX was significantly associated with a higher proportion of those receiving full DI and for those treated with FOLFIRI/NAB G-CSF was associated with a lower proportion of full DI. There was a non-significant association between full DI and increased PFS whatever the chemotherapy. These data highlight the interest of analyzing G-CSF use in clinical trials. Future studies that include more patients and/or other chemotherapy regimens (FLOT, DCF, FOLFOXIRI, etc.) could confirm these data and determine the interest of and best protocols for G-CSF use in digestive oncology.

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Conflict of Interest

Julien Taieb: Roche, Merck KGaA, Amgen, Lilly, MSD, Servier, Pierre Fabre, Sanofi, Samsung (C/A), Merck, Roche, Amgen, Lilly, Sanofi, Samsung, MSD, Servier, Celgene, Pierre Fabre (H), Servier, Amgen, Roche, Sanofi, Merck, Lilly, Pierre Fabre (Other—Speaker's bureau); **Laetitia Dahan**: Amgen, Baxalta, Celgene, Lilly, Merck, Sanofi and Roche (C/A), Celgene, Ipsen, Sanofi (Travel grants), Ipsen, Lilly, MSD, Sanofi (RF); **Anthony Lopez:** Roche (RF), Amgen (C/A), Vifor Pharma, Bayer, Merck, Sanofi, Ipsen (H, lecture fees), Abbvie, Amgen, MSD, Vifor-Pharma, Mundi Pharma, Ipsen, Novartis (Travel expenses unrelated to this work); **Jean-Baptiste Bachet**: Amgen, AstraZeneca, Bayer, Merck Serono, Pierre Fabre, Servier (C/A), Amgen, AstraZeneca, Bayer, Merck Serono, Pierre Fabre, Roche, Sanofi, Servier (H). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board.

Author Contributions

Conception/design: O.B., M.B., C.L., J.-B.B. Provision of study material/patients: K.L.M., J.-B.B. Collection and/or assembly of data: C.C., K.L.M., J.T., L.D., J.-B.B. Data analysis and interpretation: C.C., O.B., M.B., C.L., J.-B.B. Manuscript writing: C.C., O.B., M.B., K.L.M., J.T., L.D., A.L., C.L., J.-B.B. Final approval of manuscript: all authors.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Supplementary Material

Supplementary material is available at *The Oncologist* online.

References

1. Burris HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol*. 1997;15:2403-2413. https://doi.org/10.1200/JCO.1997.15.6.2403
2. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364:1817-1825. https://doi.org/10.1056/NEJMoa1011923
3. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369:1691-1703. https://doi.org/10.1056/NEJMoa1304369
4. National Cancer Institute Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events (CTCAE). Available at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40. Accessed March 5, 2021.
5. Bosly A, Bron D, Van Hoof A, et al. Achievement of optimal average relative dose intensity and correlation with survival in diffuse large B-cell lymphoma patients treated with CHOP. *Ann Hematol*. 2008;87:277-283. https://doi.org/10.1007/s00277-007-0399-y
6. Chirivella I, Bermejo B, Insa A, et al. Optimal delivery of anthracycline-based chemotherapy in the adjuvant setting improves outcome of breast cancer patients. *Breast Cancer Res Treat*. 2009;114:479-484. https://doi.org/10.1007/s10549-008-0018-1
7. Radosavljevic D, Golubicic I, Gavrilovic D, et al. Do the time to chemotherapy response and the dose intensity have an impact on patient outcome in advanced non-small cell lung cancer? *J BUON*. 2009;14:203-209.
8. Sarosy GA, Hussain MM, Seiden MV, et al. Ten-year follow-up of a phase 2 study of dose-intense paclitaxel with cisplatin and cyclophosphamide as initial therapy for poor-prognosis, advanced-stage epithelial ovarian cancer. *Cancer* 2010;116:1476-1484. https://doi.org/10.1002/cncr.24861
9. Green MD, Koelbl H, Baselga J, et al. A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. *Ann Oncol*. 2003;14:29-35. https://doi.org/10.1093/annonc/mdg019
10. Gisselbrecht C, Haioun C, Lepage E, et al. Placebo-controlled phase III study of lenograstim (glycosylated recombinant human granulocyte colony-stimulating factor) in aggressive non-Hodgkin's lymphoma: factors influencing chemotherapy administration. Groupe d'Etude des Lymphomes de l'Adulte. *Leuk Lymphoma*. 1997;25:289-300. https://doi.org/10.3109/10428199709114168
11. Aapro MS, Cameron DA, Pettengell R, et al. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. *Eur J Cancer*. 2006;42:2433-2453. https://doi.org/10.1016/j.ejca.2006.05.002
12. Aapro MS, Bohlius J, Cameron DA, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. *Eur J Cancer*. 2011;47:8-32. https://doi.org/10.1016/j.ejca.2010.10.013
13. Klastersky J, de Naurois J, Rolston K, et al. Management of febrile neutropaenia: ESMO clinical practice guidelines. *Ann Oncol*. 2016;27:v111-v118. https://doi.org/10.1093/annonc/mdw325
14. 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;33:3199-3212. https://doi.org/10.1200/JCO.2015.62.3488
15. Chen P, Lei J, Wu Y, et al. Pegylated G-CSF combined with mFOLFIRINOX for advanced pancreatic cancer patients. *Intern Med*. 2020;59:877. https://doi.org/10.2169/internalmedicine.3790-19
16. Yamao K, Takenaka M, Yoshikawa T, et al. Clinical safety and efficacy of secondary prophylactic pegylated G-CSF in advanced pancreatic cancer patients treated with mFOLFIRINOX: a single-center retrospective study. *Intern Med*. 2019;58:1993-2002. https://doi.org/10.2169/internalmedicine.2234-18
17. Ninomiya R, Nakazawa A, Miyata Y, et al. Primary prophylactic administration of pegfilgrastim in FOLFIRINOX therapy for locally advanced pancreatic carcinoma. *Gan To Kagaku Ryoho* 2016;43:1678-1680.
18. Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or gemcitabine as adjuvant therapy for pancreatic cancer. *N Engl J Med*. 2018;379:2395-2406. https://doi.org/10.1056/NEJMoa1809775
19. Dahan L, Williet N, Le Malicot K, et al. Randomized phase II trial evaluating two sequential treatments in first line of metastatic pancreatic cancer: results of the PANOPTIMOX-PRODIGE 35 trial. *J Clin Oncol*. 2021;39:3242-3250.
20. Rinaldi Y, Pointet A-L, Khemissa Akouz F, et al. Gemcitabine plus nab-paclitaxel until progression or alternating with FOLFIRI.3, as first-line treatment for patients with metastatic pancreatic adenocarcinoma: The Federation Francophone de Cancérologie Digestive-PRODIGE 37 randomised phase II study (FIRGEMAX). *Eur J Cancer*. 2020;136:25-34. https://doi.org/10.1016/j.ejca.2020.05.018
21. Bachet J-B, Hammel P, Desramé J, et al. Nab-paclitaxel plus either gemcitabine or simplified leucovorin and fluorouracil as first-line therapy for metastatic pancreatic adenocarcinoma (AFUGEM GERCOR): a non-comparative, multicentre, open-label, randomised phase 2 trial. *Lancet Gastroenterol Hepatol* 2017;2:337-346. https://doi.org/10.1016/S2468-1253(17)30046-8
22. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70:41-55. https://doi.org/10.1093/biomet/70.1.41
23. D'Agostino RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 1998;17:2265-2281. https://doi.org/10.1002/(sici)1097-0258(19981015)17:19<2265::aid-sim918>3.0.co;2-b
24. Bates D, Kliegl R, Vasishth S, et al. Parsimonious mixed models. arXiv: 1506.04967v2 [stat.ME] 2018. Available at: http://arxiv.org/abs/1506.04967v2.
25. Austin PC. A tutorial on multilevel survival analysis: methods, models and applications. *Int Stat Rev*. 2017;85:185-203. https://doi.org/10.1111/insr.12214
26. Pettengell R, Gurney H, Radford JA, et al. Granulocyte colony-stimulating factor to prevent dose-limiting neutropenia in non-Hodgkin's lymphoma: a randomized controlled trial. *Blood* 1992;80:1430-1436.
27. Leonard RCF, Mansi JL, Keerie C, et al. A randomised trial of secondary prophylaxis using granulocyte colony-stimulating factor ('SPROG' trial) for maintaining dose intensity of standard adjuvant chemotherapy for breast cancer by the Anglo-Celtic Cooperative Group and NCRN. *Ann Oncol*. 2015;26:2437-2441. https://doi.org/10.1093/annonc/mdv389
28. Sternberg CN, Mulder PHM de, Schornagel JH et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer Protocol No. 30924. *J Clin Oncol* 2016. https://doi.org/10.1200/JCO.2001.19.10.2638
29. Bohlius J, Herbst C, Reiser M, et al. Granulopoiesis-stimulating factors to prevent adverse effects in the treatment of malignant lymphoma. *Cochrane Database Syst Rev*. 2008;(4):CD003189. https://doi.org/10.1002/14651858.CD003189.pub4
30. Lal A, Bhurgri Y, Rizvi N, et al. Factors influencing in-hospital length of stay and mortality in cancer patients suffering from febrile neutropenia. *Asian Pac J Cancer Prev*. 2008;9:303-308.
31. Lyman GH, Dale DC, Culakova E, et al. The impact of the granulocyte colony-stimulating factor on chemotherapy dose inten-

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sity and cancer survival: a systematic review and meta-analysis of randomized controlled trials. *Ann Oncol*. 2013;24:2475-2484. https://doi.org/10.1093/annonc/mdt226

32. Kawahira M, Yokota T, Hamauchi S, et al. Primary prophylactic granulocyte colony-stimulating factor according to ASCO guidelines has no preventive effect on febrile neutropenia in patients treated with docetaxel, cisplatin, and 5-fluorouracil chemotherapy. *Int J Clin Oncol*. 2018;23:1189-1195. https://doi.org/10.1007/s10147-018-1306-3
33. Pinter T, Klippel Z, Cesas A, et al. A phase III, randomized, double-blind, placebo-controlled trial of pegfilgrastim in patients receiving first-line FOLFOX/bevacizumab or FOLFIRI/bevacizumab for locally advanced or metastatic colorectal cancer: final results of the pegfilgrastim and anti-VEGF evaluation study (PAVES). *Clin Colorectal Cancer*. 2017;16:103-114.e3. https://doi.org/10.1016/j.clcc.2016.08.008
34. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol*. 2006;24:3187-3205. https://doi.org/10.1200/JCO.2006.06.4451
35. Base de données publique des médicaments. Available at http://base-donnees-publique.medicaments.gouv.fr/. Accessed May 24, 2020.
36. Luo G, Guo M, Liu Z, et al. Blood neutrophil-lymphocyte ratio predicts survival in patients with advanced pancreatic cancer treated with chemotherapy. *Ann Surg Oncol*. 2015;22:670-676. https://doi.org/10.1245/s10434-014-4021-y
37. Guo J, Wu M, Guo L, et al. Pretreatment blood neutrophil/lymphocyte ratio is associated with metastasis and predicts survival in patients with pancreatic cancer. *Bull Cancer*. 2018;105:146-154. https://doi.org/10.1016/j.bulcan.2017.10.028

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