JNCI Cancer Spectrum (2021) 5(5): pkab074

doi: 10.1093/jncics/pkab074
First published online 23 August 2021
Article

Dosing Schedules of Gemcitabine and nab-Paclitaxel for Older Adults With Metastatic Pancreatic Cancer

Arthur Winer, MD,[1,2,*] Elizabeth Handorf, PhD,[3] Efrat Dotan, MD[1]

[1]Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA, [2]Department of Medical Oncology, Inova Schar Cancer Institute, Fairfax, VA, USA, and [3]Department of Biostatistics, Fox Chase Cancer Center, Philadelphia, PA, USA

*Correspondence to: Arthur Winer, MD, Inova Schar Cancer Institute, 8081 Innovation Park Drive, Fairfax, VA 22031 USA (e-mail: arthur.winer@inova.org).

Abstract

Background: Gemcitabine and nab-paclitaxel (GA) is a first-line treatment for patients with metastatic pancreatic cancer (mPDAC). The traditional dosing schedule of GA is days 1, 8, and 15 of a 28-day cycle. Frequently, older adults are given a modified dosing schedule using 2 doses per cycle because of toxicity. We retrospectively analyzed treatment patterns and outcomes of older adults with mPDAC given these 2 dosing schedules. **Methods:** Patients 65 years or older with mPDAC treated with GA in a nationwide real-world database between January 1, 2014, and May 31, 2019, were included. Demographic, disease, and treatment information were collected. Patients were grouped by dosing at treatment initiation (traditional vs modified dosing schedules). Endpoints were time on treatment (TOT) and overall survival (OS) in patients receiving at least 2 cycles. All statistical tests were 2-sided. **Results:** 1317 patients were included (traditional dosing schedule: n = 842; modified dosing schedule: n = 475). Median age at diagnosis was 72 and 73 years for traditional and modified dosing schedules, respectively ($P < .001$), but sex, race, and performance status were not statistically significantly different. The median TOT and OS were better for the traditional vs modified dosing schedule (unadjusted median TOT, first-line = 4.18 vs 3.26 mo, $P = .04$; OS = 9.44 vs 7.63 mo, $P = .003$). **Conclusion:** In this real-world cohort, treatment of older mPDAC patients with a modified dosing schedule of GA resulted in shorter TOT and worse OS vs a traditional dosing schedule. With the caveats of potential confounding that exist in a nonrandomized retrospective database, these results suggest that dose intensity may be important, and prospective studies are necessary to ensure we treat our patients most effectively.

Pancreatic cancer is the third leading cause of cancer-related death in the United States (1). More than half of patients are diagnosed with metastatic disease and are not candidates for curative surgery. Systemic chemotherapy is the only viable treatment option for most patients diagnosed with metastatic pancreatic cancer (mPDAC). The incidence of pancreatic cancer increases with age, with median age at diagnosis of 70 years and more than 60% of newly diagnosed patients aged older than 65 years (2). This demographic is expected to rise over the next 20 years with the aging baby boomer population, yet geriatric patients remain clinically and statistically significantly underrepresented in clinical trials (3-5).

For years, the standard treatment for mPDAC was single agent gemcitabine (6). However, 5-fluorouracil (5FU), leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) statistically significantly increased progression-free survival (PFS) and overall survival (OS) in the Accord 11 trial, establishing it as a first-line therapy (7). In 2013, the MPACT study showed an improved survival with gemcitabine plus nab-paclitaxel (GA) vs gemcitabine alone introducing another valid front-line option (8). With all of the caveats of a cross-trial comparison, FOLFIRINOX seems to provide a more robust OS vs GA, although at the expense of increased toxicity. Although both trials enrolled patients aged 65 years and older, most were younger, making it difficult to extrapolate these results for older adults. Given the increased toxicity of FOLFIRINOX and lack of patients older than 75 years enrolled in the original trial, oncologists frequently forgo treating older adults with this regimen and use GA in the frontline. However, the GA regimen also carries increased rates of grade 3 or higher toxicities, especially when used in the traditional dosing schedule (8).

Several studies have tested the feasibility of modified dosing strategies for GA. Single institution trials have successfully given this regimen on days 1 and 15 of a 28-day cycle, omitting day 8 with slight improvement in OS and PFS as compared with the original trial (9-11). Because older patients are at increased risk of toxicity from chemotherapy, dose reductions and

Received: 18 April 2021; **Revised:** 4 June 2021; **Accepted:** 18 August 2021

treatment interruptions are common (12,13), therefore, the modified GA dosing approach is an attractive option for frailer, older adults with mPDAC. However, evidence-based data are lacking to support this approach (8,11). We therefore sought to compare the tolerance and outcomes of a traditional vs modified dosing schedule of GA among patients aged 65 years and older treated at centers using an electronic health record (EHR)—derived real-world database.

Methods

Design

Through an institutional review board–approved protocol, we analyzed the nationwide Flatiron Health EHR-derived de-identified database, a longitudinal, geographically, and demographically diverse database that contains normalized, aggregated, and harmonized patient-level structured and unstructured data obtained via technology-enabled chart abstraction (14,15). At the time of this study, the database contained data from more than 250 community and academic cancer clinics, representing more than 2 million patients across the United States. Patients aged 65 years and older with mPDAC treated between January 1, 2014, and May 31, 2019, were included. These included patients with stage IV disease at presentation as well as patients with recurrent disease following definitive therapy. All patients received GA at any line for 2 or 3 doses during their first cycle (28 days) and had an office visit or started treatment within 90 days of diagnosis. Patients who received 2 doses per cycle (modified dosing schedule) included those treated with GA on 2 weeks on, 2 weeks off schedule or on every other week basis. Traditional dosing schedule patients included patients who received 3 doses of GA over a 28-day period, either as described in the MPACT trial with treatment on days 1, 8, and 15 or on days 1 and 8 followed by a week break with cycle length shortened to 21 days. Patients' treatment schedule was categorized according to the schedule used during the first cycle of treatment (3 infusions [traditional dosing schedule] vs 2 infusions [modified dosing schedule] per 28-day cycle), as this is as close as possible to an intent-to-treat definition in this retrospective dataset. Exclusion criteria included histologic diagnosis other than pancreatic adenocarcinoma and receipt of only 1 dose of GA within the first cycle of treatment.

Patient characteristics including age, sex , race, insurance type, prior surgery, Eastern Cooperative Oncology Group performance status (PS) at treatment initiation with GA, and tobacco use were obtained. Any tobacco use was considered positive. Disease and treatment information included stage at diagnosis, line of treatment, GA dosing, date of initiation and dose administration, number of cycles administered, date of treatment discontinuation, and date of progression, as well as date of last follow-up and/or death. Dose reduction at initiation was considered as any reduction of 20% or more from standard dosing of gemcitabine 1000 mg/m^2 or nab-paclitaxel 125 mg/m^2 as originally defined in the MPACT study (8). The primary objective of the study was to test for noninferiority of time on treatment (TOT; defined as time from first dose given until last dose given) and overall survival (OS; defined as time from first dose given until date of last follow-up or death) of the modified vs the traditional dosing schedule.

Statistical Analysis

Analytic variables were characterized using standard descriptive statistics (eg, means, medians, standard deviations, frequencies, and percentages). We tested for associations between dosing schedule and covariates of interest. Discrete variables were analyzed using Fisher exact test and continuous variables using Wilcoxon tests. We assessed the relationship between dosing schedule, toxicities, and dose reductions using Fisher exact tests.

We then described the association between dose schedule and survival outcomes TOT and OS in the real-world cohort using Kaplan-Meier curves. Survival analyses were stratified by line of therapy (first-line vs $\geq$ second-line), and we tested associations using log-rank tests. A Cox model tested noninferiority of the modified vs the traditional dosing schedule for TOT and OS, adjusting PS, age, race, sex, and line of therapy. Missing data was coded as a separate category for the covariates in the Cox model. The proportional hazards assumption was assessed via a test of the Schoenfeld residuals. The prespecified noninferiority upper bound was a hazard ratio (HR) of 1.2. If we failed to reject noninferiority, we then performed standard (superiority) hypothesis testing. We calculated conditional TOT and OS in patients who received at least 2 cycles and stratified by how many doses they received in the first and second cycles. To address early discontinuations, we considered the conditional survival analysis as the primary model testing study noninferiority hypotheses. TOT and OS for the whole cohort was performed in a secondary analysis. We considered 2-sided P values less than .05 to be statistically significant.

Results

Patient Characteristics

The pancreatic cancer real-world cohort included 7603 patients; 3255 (42.8%) patients received GA at some point in their treatment course. After excluding patients with other dosing patterns (n = 830), those younger than 65 years (n = 1065), and those with no visits or treatment within 90 days (n = 43), 1317 patients met inclusion criteria; 842 were treated with the traditional dosing schedule and 475 with the modified dosing schedule (Table 1). The median age at diagnosis was slightly older in the modified dosing schedule group (median age of 72 [range = 65-85] years for the traditional dosing schedule and 73 [range = 65-84] years for the modified dosing schedule; $P < .001$). A greater percentage of patients aged older than 75 years were treated with the modified (45.9%) vs the traditional dosing schedule (38.1%), however, this difference was not statistically significant ($P = .11$). Although the PS was not available for approximately 20% of patients, slightly more than 60% of patients in both groups had a PS of 0-1, which was similar between groups ($P = .07$). Greater than 80% of patients in both groups (83% traditional dosing schedule, 81.3% modified dosing schedule) were treated in the first-line setting (Table 1). In univariate analysis, there was no statistically significant difference in the sex, race, stage at diagnosis, prior surgery, tobacco use, or line of therapy between groups.

Dose Reductions and Treatment Discontinuation

Therapy was more frequently discontinued after 1 cycle in patients treated with the modified vs the traditional dosing schedule in the first-line setting (37.8% vs 10.5%; $P < .001$), and these results were consistent in the second line (23.6% vs 10.3%; $P = .01$). Dose reductions were frequent in both treatment groups (Table 2). Among all patients treated with GA, those who received the modified dosing schedule were more likely to start with a dose reduction of gemcitabine compared with those

Table 1. Patient characteristics

Characteristic	Dosing schedule		P[a]
	Traditional	Modified	
Total, No. (%)	842 (64)	475 (36)	
Median age at diagnosis (range), y	72 (65-85)	73 (65-85)	<.001
65-70	268 (31.8)	131 (27.6)	.11
70-75	245 (29.1)	126 (26.5)	
75-80	210 (24.9)	136 (28.6)	
>80	119 (14.1	82 (17.2)	
Gender, No. (%)			
Male	429 (50.9)	250 (52.6)	.60
Female	413 (49.1)	225 (47.4)	
Race, No. (%)			
White	601 (71.3)	353 (74.3)	.45
Black	64 (7.6)	42 (8.8)	
Hispanic	36 (4.2)	15 (3.2)	
Other	65 (7.8)	30 (6.3)	
Unknown	76 (9.0)	34 (7.2)	
Insurance type, No. (%)			
Commercial	277 (32.9)	159 (33.5)	.35
Medicare	259 (30.8)	126 (26.5)	
Medicaid	28 (3.3)	12 (2.5)	
Medicare/commercial	212 (25.2)	138 (29.1)	
Unknown	66 (7.7)	40 (8.4)	
Stage at diagnosis, No. (%)			
I-III	216 (25.7)	146 (30.7)	.06
IV	626 (74.3)	329 (69.3)	
Performance status, No. (%)			
0-1	530 (62.9)	289 (60.8)	.07
≥2	104 (12.4)	80 (16.8)	
Unknown	208 (24.7)	106 (22.3)	
Any smoking history, No. (%)	482 (57.2)	273 (57.5)	.98
Prior cancer surgery, No. (%)	171 (20.3)	85 (17.9)	.32
Line of treatment, No. (%)			
First-line	697 (82.8)	386 (81.3)	.25
≥ Second-line	145 (17.2)	85 (18.7)	

[a]P values calculated by univariate analysis. All tests were 2-sided.

receiving traditional dosing schedule (31.6% vs 19.8%; $P < .001$); initial dose reductions of nab-paclitaxel were similar between the 2 groups (28.6% vs 30.9%; $P = .41$).

In those patients who received at least 2 cycles of GA, on treatment dose reductions were not statistically different between modified or traditional dosing schedule patients with 35% of patients in both groups requiring a dose reduction of both agents during treatment (Table 2). As represented in the alluvial plot (Figure 1), only 40.3% (339 of 842) of all patients who initiated on traditional dosing schedule were able to complete at least 3 cycles at the same schedule, and this percentage decreased further over time, with only 14.3% (120 of 842) of patients staying on traditional dosing schedule through 6 cycles. In both groups, 38.8% of patients discontinued GA by cycle 3, and 71.5% had discontinued GA by cycle 6.

Efficacy Analysis

Given that 37.8% of patients discontinued GA after 1 cycle in the modified dosing schedule group, we decided to specifically evaluate patients who received at least 2 cycles of GA and assessed TOT and OS by conditional analysis to more accurately determine effects on overall survival (n = 864 in the front-line setting; n = 178 in the ≥ second-line setting; Figure 2, A-D). Patients treated with the traditional dosing schedule for at least 2 doses had a longer median TOT compared with those who were treated with the modified dosing schedule (4.18 mo vs 3.26 mo; $P = .04$; Figure 2, A). These results were consistent for median TOT in the second-line (traditional vs modified dosing schedule: 3.29 mo vs 2.80 mo; $P = 1.0$; Figure 2, B), as well as on multivariate analysis, adjusting for age at diagnosis, sex, race, insurance status, stage at diagnosis, PS, tobacco use, and prior pancreatic cancer surgery (Table 3).

Conditional median OS in the first-line was statistically significantly better in those who started and remained on a traditional dosing schedule vs those who were treated with a modified dosing schedule (9.44 mo vs 7.63 mo; $P = .003$; Figure 2, C). This conditional survival benefit was not seen in the second-line or later line of therapy although the small number of patients in each group limits definitive conclusions (traditional vs modified dosing schedule: 7.11 mo vs 7.11 mo; $P = .20$; Figure 2, D). Results were consistent on adjusted analysis (Table 3). Prespecified noninferiority criterion (HR = 1.2) was not met for either TOT or OS.

We analyzed the full cohort for TOT and OS difference between individuals treated with 3 vs 2 doses per cycle. TOT in the front-line remained statistically significantly longer in those treated with the traditional vs the modified dosing schedule (3.68 mo vs 1.55 mo; $P < .001$; Supplementary Figure 1, A, available online), with similar trend in the second or later line (2.99 vs 2.3 mo; $P = .40$; Supplementary Figure 1, B, available online). In a multivariate adjusted analysis, modified dosing schedule was associated with decreased TOT and was inferior to the traditional dosing schedule (HR = 1.65, 95% confidence interval [CI] = 1.44 to 1.89). The effect of modified dosing schedule on TOT was attenuated in the second or later line but still did not meet noninferiority (HR = 1.10, 95% CI = 0.81 to 1.50).

The median OS from initiation of GA to date of death or last follow-up was statistically significantly longer in the traditional vs modified dosing schedule group for the entire cohort (8.82 vs 4.67 mo; $P < .001$; Supplementary Figure 1, C, available online) in the first-line, with similar trend in the second or later line (6.78 vs 5.82 mo; $P = .05$; Supplementary Figure 1, D, available online). The modified dosing schedule was associated with shorter OS (HR = 1.66, 95% CI = 1.43 to 1.92). The effect of the modified dosing schedule on OS was attenuated but consistent in the later line setting (HR = 1.25, 95% CI = 0.89 to 1.76).

Discussion

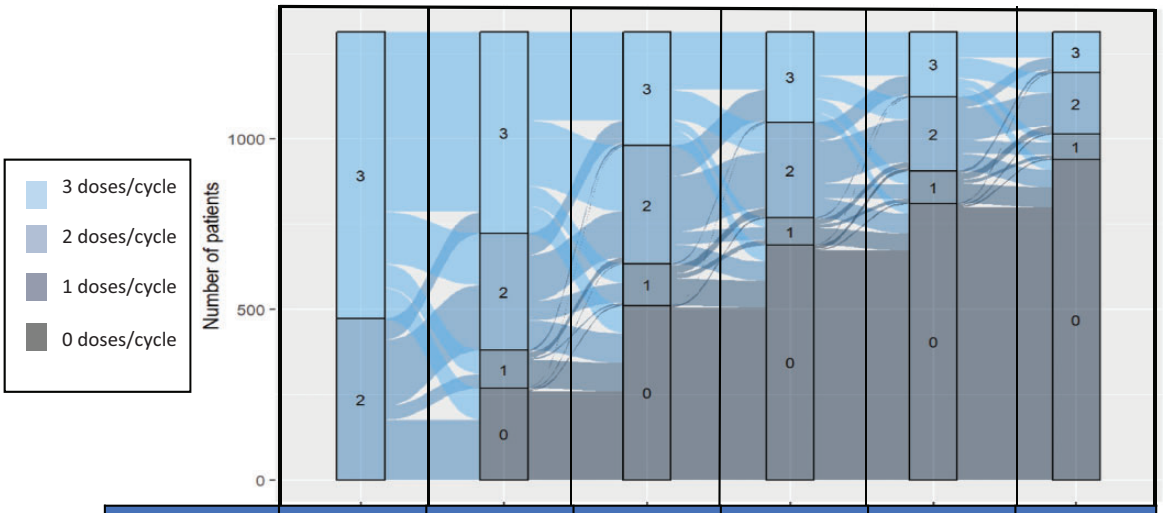
This study of more than 1300 patients describes the real-world experience and practice patterns of caring for older mPDAC patients in the United States. Gemcitabine and nab-paclitaxel is a commonly employed regimen in the setting of mPDAC and is 1 of only 2 front-line regimens recommended in the National Comprehensive Cancer Network guidelines (16). Although dose omissions of GA are common in real-world practice, our study raises questions regarding the ability of this approach to reduce toxicity while maintaining the same efficacy.

Long-term survivors have been identified in adults with mPDAC treated with weekly GA (8,16,17). A recent study of GA in patients with a PS of 2 demonstrated an acceptable safety profile, most of whom were aged older than 65 years, making this regimen a go-to in older adults (18). In the MPACT trial, the median OS was 8.5 months for GA vs 6.7 months for gemcitabine alone (17). Indeed, our study demonstrates a real-world OS of 8.82 months in traditional dosing schedule–treated patients,

Table 2. Dose reductions in all lines of therapy

Drug	Dosing schedule		P[a]
	Traditional (n = 842; 63.9%)	Modified (n = 475; 36.1%)	
Starting dose reduction, >20%, No. (%)			
Gemcitabine	167 (19.8)	150 (31.6)	<.001
Nab-paclitaxel	241 (28.6)	147 (30.9)	.41
Both drugs	127 (15.1)	102 (21.5)	.004
Dose reduction over treatment, >20%: 2 or more cycles received, No. (%)			
Gemcitabine	175 (23.2)	75 (24.4)	.75
Nab-paclitaxel	223 (29.6)	96 (31.2)	.66
Both drugs	270 (35.8)	108 (35.1)	.87

[a]Statistical significance was assessed using a 2-sided χ^2 test.



Dosing schedule	Cycle 1 No. (%)	Cycle 2 No. (%)	Cycle 3 No. (%)	Cycle 4 No. (%)	Cycle 5 No. (%)	Cycle 6 No. (%)
3 doses/cycle	842 (63.9)	591 (44.8)	334 (25.3)	266 (20.2)	191 (14.5)	120 (9.1)
2 doses/cycle	475 (36.1)	346 (26.2)	349 (26.5)	218 (16.6)	218 (16.6)	180 (13.7)
1 dose/ cycle	0	112 (8.5)	122 (9.3)	81 (6.2)	96 (7.3)	76 (5.8)
0 doses/cycle	0	268 (20.3)	512 (38.9)	689 (52.3)	812 (61.7)	941 (71.5)
Total = 1317						

Figure 1. Alluvial plot of patients treated with doses per cycle of gemcitabine and nab-paclitaxel over the course of 6 cycles. The graph represents the number of doses received during cycles 1-6 per patient. Dosing changes are represented by the changes in color over time, and the number of patients who received each dose per cycle are listed at the bottom of the figure.

essentially the same achieved in the original trial. Although we expected our analysis to demonstrate noninferiority between the dosing regimens and lend evidence to support this common practice, our results were unexpected. Patients treated with a modified dosing schedule had inferior outcomes vs those treated with a traditional dosing schedule, with about 2 months shorter median OS of 7.6 months. These results were consistent across lines of therapy, and the prespecified noninferiority criteria were not met.

The survival in those traditional dosing schedule patients who were able to tolerate at least 2 cycles of therapy was 9.97 months, implying that dose intensity and dose exposure may play an important role in controlling pancreatic adenocarcinoma. Recent retrospective data suggest that a higher dose intensity correlates with an improvement in survival in patients treated with GA, further supporting our results (19). However, as our study is retrospective, selection bias may have confounded these findings, as patients deemed fitter by their oncologist are likely the ones to receive the traditional dosing schedule and the lack of data on factors that led to these treatment decisions limits our analysis. In fact, a survival of more than 7 months may be reasonable in a group requiring up-front dose modification if those patients were frailer at baseline.

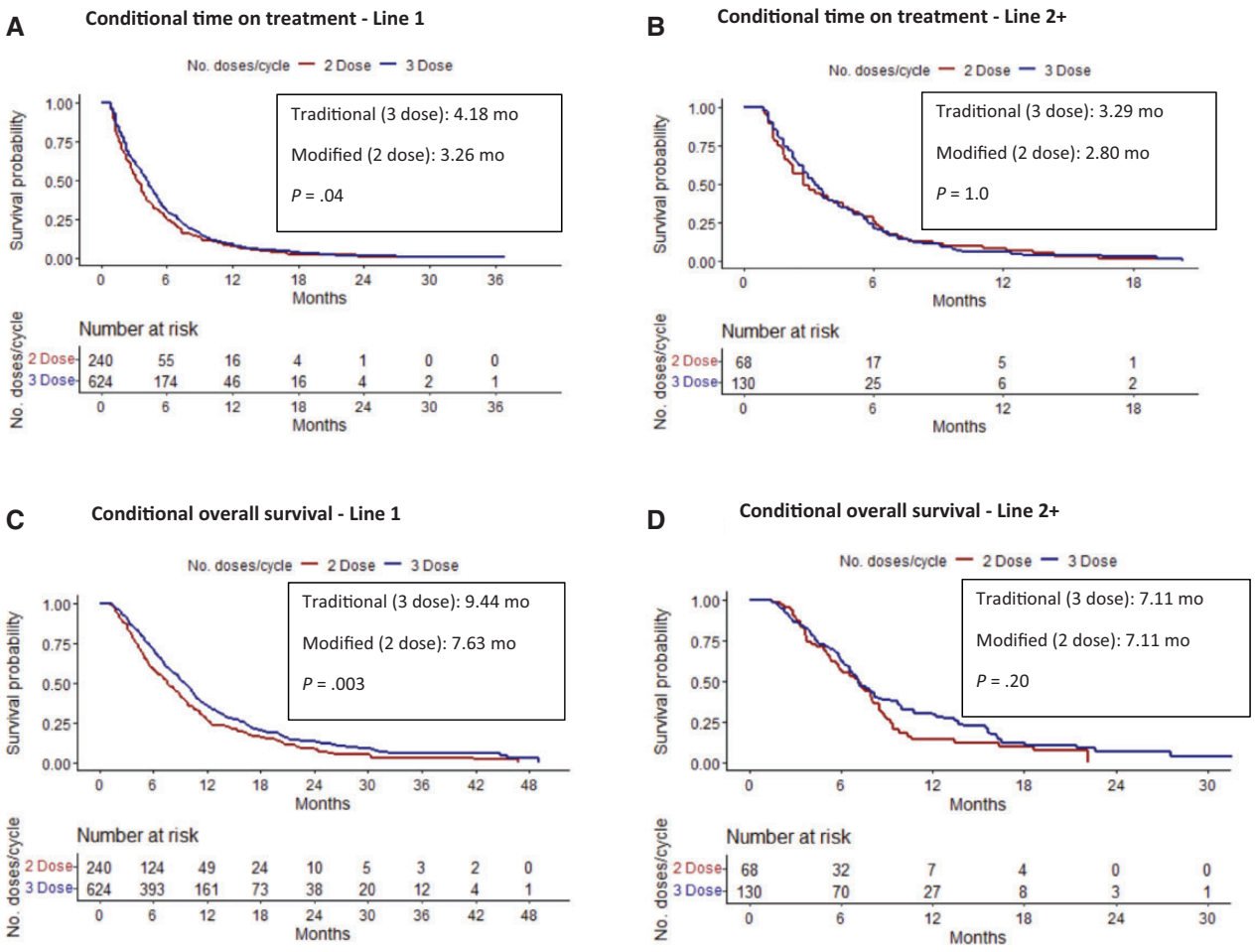


Figure 2. Conditional analysis time on treatment and overall survival. **A)** Conditional time on treatment (TOT) for patients treated with at least 2 cycles of gemcitabine and nab-paclitaxel (GA) in the first-line with the traditional dosing schedule (3 doses per cycle) vs the modified dosing schedule (2 doses per cycle) with GA. **B)** Conditional TOT for patients treated in the second-line or later line with at least 2 cycles of the traditional vs modified dosing schedule of GA. **C)** Overall survival of first-line treatment patients with at least 2 doses of the traditional vs modified dosing schedule. **D)** OS of second-line treatment patients with at least 2 doses of the traditional vs modified dosing schedule. Statistical significance was assessed using a 2-sided χ^2 test.

Although data published by Ahn et al. (11) retrospectively demonstrated the sustained efficacy of a modified dosing schedule of GA, that study was performed in a small 79-patient cohort as young as 41 (median age 64) years. Another retrospective analysis of a prospective cohort of older adults treated with GA demonstrated equivalent toxicity and efficacy of this regimen in those aged older than 70 years vs younger than 70 years (OS of 10.8 vs 10.9 months; P = .99), but numbers were small (n = 156) (20). Our analysis is the first large-scale, real-world data analysis of patients aged 65 years and older demonstrating that more than one-third of patients are being started on a modified dosing schedule of GA in the front-line setting. An estimated 1 in 5 adults will be older than 65 years by 2030, and clinical trials to guide their treatment are desperately needed (21-23). A US Food and Drug Administration analysis of clinical trial enrollment in cancer found that only 9% of clinical trial participants are older than age 75 years despite the fact that they make up 60% of all new cancer cases (24). This trend has continued, and in pancreatic cancer in particular, the rate of older adults enrollment in clinical trials has remained stagnant (5,25). A geriatric patient's true ability to tolerate oncologic treatment is often poorly assessed in real-world practice. Although tools such as the geriatric assessment and chemotherapy toxicity prediction models have been validated to help better delineate which patients will tolerate therapy, studies have shown that oncologists rarely use these tools and rely on their gestalt when it comes to treatment selection and dose adjustment (26-28). Therefore, studies are needed to further guide treatment in older patients with advanced pancreatic cancer; indeed, groups at the national level have already called for changes to clinical trials to include older adults (29).

Despite the retrospective nature of our analysis, it adds much needed data to guide the treatment of this vulnerable group of patients in the setting of lack of elderly specific prospective trials. Big data and predictive analytics have emerged in the past decade as strategies to mine real-world datasets in an effort to analyze population-level data, forecast health outcomes, and improve patient risk stratification (30-33). Although large cancer registry datasets such as the Surveillence, Epidemiology, and End Results database have existed for years allowing population-level analysis of cancer patients, only recently has EHR-derived information been gathered to form real-world datasets (14,23). These EHR-derived datasets provide information on treatment patterns and outcomes outside of a trial

Table 3. Conditional time on treatment and overall survival multivariate analysis

Characteristic	Time on treatment		Overall survival	
	HR (95% CI)		HR (95% CI)	
	First-line	Second-line or later	First-line	Second-line or later
Median age at diagnosis, y	1.00 (0.98 to 1.01)	1.00 (0.97 to 1.03)	0.99 (0.97 to 1.01)	1.00 (0.96 to 1.04)
Sex				
Male	1.00 (0.86 to 1.01)	1.08 (0.74 to 1.57)	0.95 (0.80 to 1.14)	1.40 (0.88 to 2.12)
Race				
African American	Referent	Referent	Referent	Referent
White	1.28 (0.96 to 1.71)	0.48 (0.24 to 0.94)[a]	1.09 (0.79 to 1.49)	0.58 (0.24 to 1.38)
Hispanic	1.06 (0.63 to 1.76)	0.26 (0.10 to 0.66)[a]	0.90 (0.51 to 1.60)	0.54 (0.18 to 1.61)
Other	1.40 (0.94 to 2.07)	0.39 (0.15 to 1.00)	0.86 (0.54 to 1.36)	0.37 (0.11 to 1.30)
Insurance type				
Commercial	Referent	Referent	Referent	Referent
Medicare	0.92 (0.75 to 1.12)	1.50 (0.96 to 2.34)	1.03 (0.83 to 1.28)	1.17 (0.70 to 1.95)
Medicaid	1.15 (0.74 to 1.80)	0.65 (0.24 to 1.77)	1.49 (0.90 to 2.46)	0.19 (0.04 to 0.94)[a]
Medicare/commercial	0.99 (0.81 to 1.22)	1.12 (0.70 to 1.79)	0.90 (0.71 to 1.13)	1.05 (0.61 to 1.83)
Unknown	0.76 (0.56 to 1.03)	1.11 (0.57 to 2.17)	0.69 (0.49 to 0.97)	1.39 (0.69 to 2.80)
Stage at diagnosis				
IV	1.10 (0.85 to 1.42)	1.42 (0.83 to 2.44)	0.92 (0.70 to 1.21)	1.08 (0.59 to 1.96)
Performance status				
0	Referent	Referent	Referent	Referent
1	1.14 (0.94 to 1.39)	1.10 (0.65 to 1.86)	1.32 (1.06 to 1.65)[a]	1.23 (0.68 to 2.22)
≥2	1.06 (0.80 to 1.41)	1.03 (0.55 to 1.93)	1.28 (0.93 to 1.77)[a]	1.73 (0.86 to 3.49)
Unknown	1.40 (1.11 to 1.73)[a]	1.34 (0.80 to 2.44)	1.69 (1.31 to 2.18)[a]	1.41 (0.74 to 2.67)
Tobacco use	1.09 (0.93 to 1.28)	0.80 (0.53 to 1.20)	1.10 (0.92 to 1.32)	1.21 (0.76 to 1.93)
Prior cancer surgery	0.85 (0.64 to 1.14)	1.50 (0.84 to 2.66)	0.62 (0.45 to 0.84)[a]	1.26 (0.66 to 2.42)

[a]Indicates statistically significant hazard ratios (HRs). CI = confidence interval.

setting and provide the medical community a wealth of data on how oncologic patients are treated in everyday practice, including less studied populations such as the elderly.

Notably, there are some important limitations to our study given the difficulty in controlling for multiple factors in an observational dataset. The high frequency of dose reduction at treatment initiation and high number of patients who discontinued treatment after 1 cycle in the modified dosing schedule group may indicate that more frail patients were started on this treatment approach. This may represent confounding by indication, as the specific reason for selecting a modified vs a traditional dosing schedule was not clear. We are unable to determine why these patients were selected for treatment vs best supportive care from this retrospective dataset, however, our results emphasize the need to better identify those patients who would be good candidates for anticancer therapy. Frailer patients may have been deemed ineligible for the traditional dosing schedule at treatment initiation and were instead started on the modified dosing schedule, but perhaps some should have been directed toward best supportive care.

Although we attempted to address this using our conditional survival analysis, residual confounding in the more limited cohort may remain. Indeed, we were able to account for PS in most cases, however, roughly one-quarter of patients did not have PS data available. Furthermore, the Eastern Cooperative Oncology Group PS scale was validated in younger patients and does not address the aging process in its assessment and thus may not fully account for the factors contributing to the recommendations for modified vs traditional dosing schedule (26). The lack of a geriatric assessment that evaluates a patient's frailty comprehensively adds to the challenges in analyzing these data (26). Comorbidities were also not captured, which may have contributed to a shorter OS and affected treatment selection by the oncologist thereby affecting the analysis. Quality-of-life alterations may have also affected the decision to change therapy, but that information is beyond the scope of this analysis.

Other possible limitations include the reliance on data extracted from an EHR, which may also lead to errors in the abstraction process. However, we attempted to account for possible errors by analyzing structured pharmacy data that more accurately reflect drug and dose delivery. We also attempted to minimize errors in incorrectly assigning patients to a given treatment group by looking at doses delivered over the first cycle and allocating the patient to the traditional vs modified dosing schedule in an intent-to-treat fashion. This fits the typical clinical practice of most providers who will opt for dose reduction or schedule alteration based on treatment tolerance.

In summary, our study used a large data set to understand real-world treatment approaches and outcomes in older adults with mPDAC. Although this study is by no means definitive or conclusive, it does raise questions about the recommended treatment approach in the frailer geriatric population. As 35% of modified dosing schedule–treated patients discontinued treatment after only 1 cycle, better assessment of risk factors contributing to tolerability of treatment are required. We, as an oncology community, must do better to identify older adults who are less likely to benefit from our toxic treatments such as by performing a pretreatment comprehensive geriatric assessment. These results further support the need for additional prospective research to define the optimal treatment approach for older adults with mPDAC. Studies are ongoing of both

FOLFIRINOX and GA in this patient population to better define the safety and efficacy of these regimens in older adults (34,35).

Funding

Supported by a Cancer Center Support Grant 3 P30 CA006927.

Notes

The role of the funder: The funder had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

Disclosures: The authors have no relevant disclosures.

Author contributions: Arthur Winer was involved in the conceptualization, data curation, formal analysis, investigation, methodology, and writing of the original draft as well as in reviewing and editing the manuscript. Efrat Dotan was involved in the conceptualization, funding acquisition, methodology, project administration, supervision, writing of the original draft and reviewing and editing the manuscript. Elizabeth Handorf was involved in the conceptualization, data curation, formal analysis, methodology, software, writing of the original draft and reviewing and editing the manuscript.

Prior presentations: Presented at the 2020 ASCO GI Cancers Symposium in San Francisco, CA, January 23-25, 2020.

Data Availability

The data underlying this article were provided by Flatiron Health via a data sharing agreement. Data will be shared on request to the corresponding author with permission of Flatiron Health.

References

1. American Cancer Society. *Cancer Facts and Figures*; 2021: 1–72. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf. Accessed May 17, 2021.
2. American Cancer Society. Key statistics for pancreatic cancer; 2018. https://www.cancer.org/cancer/pancreatic-cancer/about/key-statistics.html. Accessed September 8, 2018.
3. Hurria A, Mohile SG, Dale W. Research priorities in geriatric oncology: addressing the needs of an aging population. *J Natl Compr Canc Netw [Netw]*. 2012;10(2):286–288.
4. Hutchins L, Unger J, Crowley J, Coltman C, Albain K. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med*. 1999; 341(27):2061–2067.
5. White M, Dotan E, Catalano P, Cardin D, Berlin J. Advanced pancreatic cancer clinical trials: the continued underrepresentation of older patients. *J Geriatr Oncol*. 2019;10(4):540–546.
6. Howard B, Iii AB, Moore MJ, 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*. 2013;15(6):2403–2413.
7. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817–1825.
8. 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(18):1691–1703.
9. Heinemann V, Quietzsch D, Gieseler F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J Clin Oncol*. 2006;24(24):3946–3952.
10. Poplin E, Feng Y, Berlin J, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2009; 27(23):3778–3785.
11. Ahn DH, Krishna K, Blazer M, et al. A modified regimen of biweekly gemcitabine and nab-paclitaxel in patients with metastatic pancreatic cancer is both tolerable and effective: a retrospective analysis. *Ther Adv Med Oncol*. 2017;9(2): 75–82.
12. Kale M, Mhango G, Gomez J, et al. Treatment toxicity in elderly patients with advanced non-small cell lung cancer. *Am J Clin Oncol*. 2017;40(5):470–476.
13. Berger AK, Haag GM, Ehmann M, Byl A, Jäger D, Springfeld C. Palliative chemotherapy for pancreatic adenocarcinoma: a retrospective cohort analysis of efficacy and toxicity of the FOLFIRINOX regimen focusing on the older patient. *BMC Gastroenterol*. 2017;17(1):143–149.
14. Pancreatic Cancer Cohort. Flatiron Health EHR-derived database; 2020. Flatiron.com. Accessed December 27, 2019.
15. Griffith SD, Miksad RA, Calkins G, et al. Characterizing the feasibility and performance of real-world tumor progression end points and their association with overall survival in a large advanced non-small-cell lung cancer data set. *J Clin Oncol Clin Cancer Inform*. 2019;(3):1–13.
16. National Comprehensive Cancer Network. *Pancreatic Adenocarcinoma*; 2021. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic_blocks.pdf. Accessed May 3, 2021.
17. Goldstein D, El-Maraghi RH, Hammel P, et al. Nab-paclitaxel plus gemcitabine for metastatic pancreatic cancer: Long-term survival from a phase III trial. *J Natl Cancer Inst*. 2015;107(2):1–10.
18. Macarulla T, Pazo-Cid R, Guillén-Ponce C, et al. Phase I/II trial to evaluate the efficacy and safety of nanoparticle albumin-bound paclitaxel in combination with gemcitabine in patients with pancreatic cancer and an ECOG performance status of 2. *J Clin Oncol*. 2019;37(3):230–238.
19. Lim A, Kim D, Kim K, Kim R, Bottiglieri S. Dose intensity of nab-paclitaxel and gemcitabine chemotherapy in metastatic pancreatic cancer. *J Clin Oncol*. 2019;37(suppl 4):251.
20. Vivaldi C, Salani F, Rovesti G, et al. First-line gemcitabine plus nab-paclitaxel for elderly patients with metastatic pancreatic cancer: Crossing the frontier of age? *Eur J Cancer*. 2020;137(2020):108–116.
21. Howlader N, Noone AM, Krapcho M, et al. National Cancer Institute SEER Cancer Statistics Review (1975-2012). Published 2015.
22. Dotan E. Advancing treatment approach to the older patient with cancer through clinical trials participation. *Surg Oncol Clin N Am*. 2017;26(4): 719–728.
23. National Cancer Institute, Surveillence, Epidemiology, and End Results (SEER) Program. Cancer stat facts: Pancreatic cancer; 2020. https://seer.cancer.gov/statfacts/html/pancreas.html. Accessed April 17, 2020.
24. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US Food and Drug Administration. *J Clin Oncol*. 2004;22(22):4626–4631.
25. Scher KS, Hurria A. Under-representation of older adults in cancer registration trials: known problem, little progress. *J Clin Oncol*. 2012;30(17):2036–2038.
26. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J Clin Oncol*. 2011; 29(25):3457–3465.
27. Mohile SG, Magnuson A, Pandya C, et al. Community oncologists' decision-making for treatment of older patients with cancer. *J Natl Compr Canc Netw*. 2018;16(3):301–309.
28. Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. *Evidence-based medicine: how to practice and teach EBM*, 2nd ed. Edinburgh: Churchill Livingstone; 2000.
29. Hurria A, Dale W, Mooney M, et al.; for the Cancer and Aging Research Group. Designing therapeutic clinical trials for older and frail adults with cancer: U13 conference recommendations. *J Clin Oncol*. 2014;32(24):2587–2594.
30. Parikh RB, Gdowski A, Patt DA, Hertler A, Mermel C, Bekelman JE. Using big data and predictive analytics to determine patient risk in oncology. *Am Soc Clin Oncol Educ B*. 2019;(39):e53–58.
31. Willems S, Abeln S, Feenstra KA, et al. The potential use of big data in oncology. *Oral Oncol*. 2019;98:8–12.
32. Ather S, Kadir T, Gleeson F. Artificial intelligence and radiomics in pulmonary nodule management: current status and future applications. *Clin Radiol*. 2020;75(1):13–19.
33. He X, Neus G, Ricard G, Marco I. Big data for the stratification of readmission risk after hospital discharge of older adults with complex conditions. *Int J Integr Care*. 2019;19(S1):1–2.
34. Clinicaltrials.gov. Efficacy and tolerance evaluation in FOLFIRINOX dose adjusted in elderly patients with a metastatic pancreatic cancer (PAMELA70); 2019. https://clinicaltrials.gov/ct2/show/NCT02143219. Accessed December 5, 2019.
35. Clinicaltrials.gov2. Geriatric Assessment directed trial to evaluate gemcitabine +/- nab-paclitaxel in elderly pancreatic cancer patients (GrantPax); 2021. https://clinicaltrials.gov/ct2/show/NCT02812992?term=NCT02812992&rank=1. Accessed May 3, 2021.