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

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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 (6).

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...
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 of therapy (first-line vs > 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.
reduced further over time, with only 14.3% (120 of 842) of at least 3 cycles at the same schedule, and this percentage initiated on traditional dosing schedule were able to complete luvial plot (Figure 1), only 40.3% (339 of 842) of all patients who P the 2 groups (28.6% vs 30.9%; P = .41). The effect of the 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).

Conditional 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.
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.

### Table 2. Dose reductions in all lines of therapy

| Drug                  | Traditional (n = 842; 63.9%) | Modified (n = 475; 36.1%) | P*  |
|-----------------------|-----------------------------|---------------------------|-----|
| 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  |

*Statistical significance was assessed using a 2-sided χ² test.

![Figure 1](https://academic.oup.com/jncics/article-fig/5/5/pkab074/6356527)

**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.
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 6% 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 Surveillance, 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.
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

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

| Characteristic               | Time on treatment | Overall survival |
|------------------------------|-------------------|------------------|
|                              | First-line HR (95% CI) | Second-line or later HR (95% CI) | First-line HR (95% CI) | Second-line or later HR (95% CI) |
|                              | 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) | 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) |
| Median age at diagnosis, y   | 1.06 (0.63 to 1.76) | 0.26 (0.10 to 0.66)* | 0.90 (0.51 to 1.60) | 0.54 (0.18 to 1.61) | 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                          | 1.00 (0.86 to 1.01) | 0.74 (0.70 to 1.79) | 1.09 (0.79 to 1.49) | 0.58 (0.24 to 1.38) | 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) |
| Race                         | 1.28 (0.96 to 1.71) | 0.48 (0.24 to 0.94)* | 0.90 (0.51 to 1.60) | 0.54 (0.18 to 1.61) | 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) |
| Performance status           | 1.28 (0.96 to 1.71) | 0.48 (0.24 to 0.94)* | 0.90 (0.51 to 1.60) | 0.54 (0.18 to 1.61) | 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) |
| Stage at diagnosis           | 1.10 (0.85 to 1.42) | 0.83 (0.70 to 1.21) | 1.32 (1.06 to 1.65)* | 1.23 (0.68 to 2.22) | 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) |
| Tobacco use                  | 1.10 (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) | 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) |
| Prior cancer surgery         | 1.08 (0.84 to 1.54) | 1.50 (0.84 to 2.66) | 1.06 (0.45 to 0.84)* | 1.26 (0.66 to 2.42) | 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) |

*Indicates statistically significant hazard ratios (HRs). CI = confidence interval.
FOLFOXIRI and GA in this patient population to better define the safety and efficacy of these regimens in older adults (34,35).

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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.

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