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Outcomes in Patients With Metastatic Pancreatic Adenocarcinoma With the Introduction of New Chemotherapeutic Drugs:

10-Year Experience of a Single NCI-designated Comprehensive Cancer Center

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Abstract

Objectives: Adenocarcinoma of the pancreas represents the third leading cause of cancer-related death in the United States. Drug combinations, FOLFIRINOX (5-FU, leucovorin, irinotecan, and oxaliplatin) and gemcitabine/nab-paclitaxel, showed a clinically meaningful benefit when compared with single-agent gemcitabine in phase III trials. The goal of this study was to investigate whether there was an increase in overall survival (OS) for patients treated for metastatic pancreatic cancer after the introduction of the above regimens.

Materials and Methods: Patients were grouped into 2 treatment eras that were before and after the introduction of these newer chemo-therapeutic regimens; 2006–2010 and 2011–2015, respectively. Baseline demographics and disease-related variables were collected from meta-static pancreatic cancer treated at the Barbara Ann Karmanos Cancer Institute in Detroit, MI.

Results: When stratified by treatment era, the later era had an improvement in survival (hazard ratio for death of 0.61; $P = 0.005$). Median OS was 8.97 and 9.95 months for the earlier ($n = 59$) versus latter era ($n = 99$), respectively. There was an increase from 28.3% to 38.9% at 12 months between the earlier and later era, an improvement of 37.4%. African Americans had a worse outcome with a hazard ratio of 1.63 ($P = 0.02$) for death. When comparing the eras, Caucasians had a longer median OS in each era in addition to having a greater improvement in median OS between eras.

Conclusions: There was a modest improvement in median OS between 2006–2010 and 2011–2015 with the introduction of newer chemo-therapeutic regimens. However, there has been no significant improvement in outcomes for African Americans or in short-term survival.

Keywords

pancreatic adenocarcinoma; FOLFIRINOX; gemcitabine; nab-paclitaxel; overall; survival; chemotherapy

Adenocarcinoma of the pancreas is one of the deadliest types of cancers and represents the third leading cause of cancer-related death in the United States.¹ It is estimated that up to 80% of patients have locally advanced or metastatic disease at the time of diagnosis, for which palliative chemotherapy remains the only viable treatment option.² Thus, considerable effort has been made in the last 3 decades to develop more effective therapies to combat pancreatic cancer.

A randomized phase III trial performed by Burris et al³ in 1997 demonstrated better overall survival (OS) for gemcitabine in comparison to intravenous bolus 5-fluorouracil (5-FU). This finding established gemcitabine as the standard of care in advanced pancreatic cancer for > 2 decades, during which various chemo-therapeutic regimens were extensively studied. Multiple drugs were subsequently added to gemcitabine, which included conventional cytotoxic drugs (5-FU, cisplatin, irinotecan, oxaliplatin, capecitabine) and targeted agents (bevacizumab, cetuximab). Unfortunately, none of the tested combinations produced a clinically worthwhile advantage over gemcitabine alone.⁴⁻⁷ However, more recently 2 combinations showed a clinically meaningful benefit when compared with single-agent gemcitabine. FOLFIRINOX (5-FU, leucovorin, irinotecan, and oxaliplatin) showed increased median OS (11.1 versus 6.8 mo) when compared with gemcitabine alone.⁸ The combination of gemcitabine and nab-paclitaxel showed superiority over gemcitabine alone with a median improvement of 1.8 months, 6.7 versus 8.5 months.⁹

This study is a retrospective analysis involving a single National Cancer Institute-designated comprehensive cancer center to determine whether the introduction and adoption of FOLFIRINOX and the Gem/nab-P regimens improved the survival of patients with metastatic pancreatic cancer and the extent of the added benefit. The goal is to determine whether there was an improvement in median OS for the overall population between an earlier and later era from patients treated in real-life practice.

MATERIALS AND METHODS

Data Collection

Clinical data including demographics, treatment received, and outcome were collected from 159 consecutive patients treated for metastatic pancreatic cancer by the gastrointestinal cancer multidisciplinary team at Barbara Ann Karmanos Cancer Institute in Detroit, MI, an National Cancer Institute-designated comprehensive cancer center. Patients were deemed eligible for this study if they had presented with metastatic disease or had localized pancreatic cancer that progressed into metastatic disease. Number of lines of treatment used after the first line was recorded into their total number of lines of therapy. The type of therapy was only recorded for the first line of treatment of metastatic disease.

Study Design

Patients were grouped into 2 treatment eras, which were considered before and after the introduction of these newer chemotherapeutic regimens, 2006–2010 and 2011–2015, respectively. Baseline characteristics were summarized and compared among the 2 subgroups. The study was approved by the Institutional Review Board at Wayne State University.

Statistical Analysis

OS was defined as the duration of time from starting the first-line treatment for metastatic disease to date of death or censor. Comparisons of abstracted variables (such as age, race, sex, and Eastern Cooperative Oncology Group performance status [PS]) between treatment eras were made using a χ^2 test (for categorical variables) and a *t* test (for continuous variables). OS was described using the Kaplan-Meier method. Variables were tested for association with OS using a Cox regression model stratifying for age (dichotomized at 65 and surgery status).

RESULTS

Patient Characteristics

Table 1 gives the patient characteristics. Demographics were well balanced in the 2 patient groups. Of the 159 patients, 76 (48%) were aged older than 65 with a range of 33 to 89. In total, 89 (55%) were male. The 119 (74%) were Caucasian, 38 (24%) were African American, 1 (1%) was Asian, and 1 (1%) was Hispanic. The 113 (71%) had an Eastern Cooperative Oncology Group PS of 0 or 1 and 46 (28%) had a PS of 2 or worse.

Survival Outcome by Treatment Era

When stratified by treatment era, the later era had an improvement in survival, having a hazard ratio (HR) of 0.61 ($P=0.003$) for death. Median (95% confidence interval) OS times for the 2006–2010 and 2011–2015 groups were 8.97 (6.0, 10.0) and 9.95 (8.1, 12.0) months, respectively. Because of the timing of the introduction of the newer regimens, there's a clear difference in number of patients treated with FOLFIRINOX from each era (Fig. 1). In total, 35 patients from the 2011–2015 era received FOLFIRINOX, whereas only 5 patients received this treatment in the 2006–2010 era. Approximately 35% of patients treated in the later era were treated with FOLFIRINOX. Those treated with FOLFIRINOX in the later era showed a significant increase in OS, having a median OS of 15.0 (11.0, 20.0) months as opposed to those not receiving FOLFIRINOX from the same era who had a median OS of 9.0 (7.0, 10.0) months (Fig. 2). Overall, those treated with FOLFIRINOX had an HR of 0.61 ($P=0.02$). The survival rates were also higher in the later era for 6, 9, and 12 months (Fig. 3). Most notably, 38.9% of patients from the later era survived 12 months, whereas 28.3% survived in the earlier era.

Impact of Ethnicity on Survival

Upon multivariable Cox regression analysis, stratifying by age dichotomized at 65 and surgery status and adjusting for stage of initial cancer diagnosis and FOLFIRINOX

treatment status, African American patients had an HR of 1.63 (1.09, 2.43), $P=0.02$, for death relative to Caucasian patients. The 31 Caucasians were treated with FOLFIRINOX, whereas 9 African Americans were treated with the same regimen. Improved median OS was seen among Caucasian patients compared with African Americans between the eras. Caucasians had an improvement in median OS from 8.97 to 9.99 months between the eras as opposed to African Americans whose median OS lowered from 8.97 to 7.98 months between the eras (Fig. 4).

DISCUSSION

Our study shows that there was a very modest increase of median overall OS of <1 month between the eras of 2006–2010 and 2011–2015 despite the adoption of potentially more efficacious combination therapies at the expense of significant increased toxicity and cost to the health care. As this is a population study as opposed to a treatment study, the number of patients treated with gemcitabine in the later era may explain the minimal increase in survival. Also, the number of gemcitabine patients is not inflated by patients on clinical trials because our institution did not participate in clinical trials utilizing a gemcitabine only treatment arm. The HR appears to be much better compared with the median OS because the HR is a summary statistic across the entire curve of data, whereas the median OS is an estimate of 1 value along the curve. In addition, the benefit of treatment may be attributed to a small subgroup of patients whose response does not translate to improvement in median OS.

FOLFIRINOX appears to be a particularly effective first-line treatment, having a median OS of 15 months. In total, 35% of patients treated in the later era were treated with FOLFIRINOX. Although, it should be noted that other factors should be taken into consideration such as those who are selected for FOLFIRINOX as their first-line treatment typically present with a better PS and at a younger age. The median age of those treated with FOLFIRINOX in the later era was 55. Compared with median ages of 69 and 64 for those treated with gemcitabine or Gem/nab-P, respectively. Typically only those with performances statuses of 0 or 1 and younger than 75 years are considered for this regimen because they are more likely to tolerate its intensity. A significant number of patients older than 65 years received gemcitabine over other treatments ($P=0.01$). Patients below 65 years had a median OS of 9 (8, 12) months and those above 65 years had a median OS of 9 (8, 10) months, showing that age alone is not a reliable marker of outcome.

Ultimately, the goal of this study was to determine whether there was an improvement in OS of the entire population as opposed to populations receiving specific treatment regimens. It has been shown that there has been an improvement of 12-month survival from 1993 to 2013 of 4.9% to 12.7% in the general population.¹⁰ This is supported by our survival numbers shown at the 12-month mark when comparing the earlier and later eras, 27.4% and 38.9% of patients, respectively.

Another significant observation made in this study was how racial factors may play into patient outcome. African Americans consistently demonstrated shorter median OS compared with Caucasians regardless of era. Our findings are supported by other studies showing that

African Americans have a 32% higher pancreatic cancer death rate than Caucasians.¹¹ In our study, we found that PS at presentation ($P = 0.85$) and chemotherapy received ($P = 0.26$) could not explain African American's shorter median OS. This could be a result of socioeconomic factors or that the pancreatic cancer of African Americans is inherently of a more aggressive nature. It has been shown that amongst African American men, risk factors such as cigarette smoking, alcohol consumption, and diabetes mellitus explains the higher incidence of pancreatic cancer.¹² But among Caucasian and African Americans with a history of heavy consumption of alcohol, the latter is still shown to have a higher relative risk of pancreatic cancer,¹³ so modifiable risk factors do not entirely account for the increased rates of mortality in African Americans. It has been posited that African Americans may have a greater genetic susceptibility to pancreatic cancer through alcohol consumption due to genetic variations in metabolism of toxic by-products. These factors may also contribute to poor outcome in African Americans. In regards to aggressiveness, it has been found that African Americans with pancreatic cancer have a higher rate of K-ras mutations than non-African Americans.¹⁴ Treatment received by African Americans may also be different. For example, it has been shown that African Americans received radiation as treatment less often than other races.¹⁵ It is evident that higher incidence and poorer outcomes for African Americans with pancreatic cancer are due to some combination of both intrinsic and extrinsic factors.

Our study has several limitations inherent in retrospective studies. In addition, this study is not a randomized controlled trial, thus treatment groups were not randomly assigned and matching of baseline features was not utilized. Therefore, patients were selected for particular treatments according to their physician's clinical judgment. For example, patients were typically only considered for FOLFIRINOX if they had a favorable PS as those with poorer PS may not be able to tolerate such an intense regimen. Also, patients lost to follow-up or who had insufficient history in their charts may differ in a significant way compared with the patients from whom data were collected. This is also a single-site study at an academic center; hence extrapolation of this information to a universal level may not be applicable. Patients presenting to academic centers may have better PSs and the opportunity to enroll in clinical trials.

Despite the aforementioned limitations discussed in the above, this study has the strength of all the data being collected from patients from a single-cancer center, meaning patients analyzed were treated similarly, under the same level of care delivery, and with an identical quality of supportive care. Although studies collected from multiple hospitals and clinics would not have the same treatment uniformity. And as opposed to the more narrow aspects that clinical trials are confined to, this study has the benefits afforded by results taken from real-life experience. In addition, the patient population in Detroit is diverse with African Americans accounting for 25% of the patients in this study. This uniqueness allowed us to investigate a race discrepancy in pancreatic cancer treatment and outcomes.

In conclusion, there has been a very modest improvement in median OS between 2006–2010 and 2011–2015 with the introduction of newer chemotherapeutic regimens such as Gem/nab-P and FOLFIRINOX. But there has been no significant improvement in outcomes for African Americans. The modest improvement in median OS can be attributed to better long-

term survival, particularly in those patients who can tolerate FOLFIRINOX. More population-based research will need to be conducted to investigate and fully understand why African Americans demonstrate poorer outcomes with pancreatic cancer. In addition, more clinical trials must be carried out to further increase the median OS for pancreatic cancer past the modest improvements showed in this study.

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FIGURE 1.

Treatments received by era, 2006–2010 versus 2011–2016. FOLFIRINOX indicates fluorouracil, leucovorin, irinotecan, and oxaliplatin; Gem/nab-P, gemcitabine and nab-paclitaxel.

FIGURE 2. Median OS by treatment regimens received by 159 patients in 2006–2010 and 2011–2015. FOLFIRINOX indicates fluorouracil, leucovorin, irinotecan, and oxaliplatin; OS, overall survival.

FIGURE 3.

Kaplan-Meier survival curve comparing earlier and later era. OS indicates overall survival.

FIGURE 4.
Median OS by race and era. OS indicates overall survival.

TABLE 1.

Characteristics of 159 Patients with Metastatic Pancreatic Cancer Treated at Barbara Ann Karmanos Cancer Institute

	N (%)		N (%)
Sex		Stage at presentation	
Male	88 (55)	1	2 (1)
Age (median, 64) (y)		2	7 (4)
<65	83 (52)	3	22 (14)
65	76 (48)	4	128 (81)
ECOG Performance		Before surgery	
Status			
0	34 (21)	No	126 (79)
1	79 (50)	Yes	33 (21)
2	29 (18)	Chemotherapy	
3	7 (4)	Gemcitabine ± Other	92 (58)
4	10 (6)	Gem/nab-P	25 (16)
Race		FOLFIRINOX	40 (25)
Caucasian	119 (74)	Other	2 (1)
African American	38 (24)	Treatment era	
Other*	2 (2)	2006–2010	60 (38)
		2011–2015	99 (62)

* Other includes Asian and Hispanic.

ECOG indicates Eastern Cooperative Oncology Group; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin; Gem/nab-P, gemcitabine and nab-paclitaxel.