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Treatment of Elderly Patients with Advanced Pancreatic Ductal Adenocarcinoma Utilizing a Metronomic Dose and Schedule of Chemotherapy: A Better Approach

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Simple Summary

Pancreatic cancer in the elderly has been, hitherto, associated with poor survival because the current "standard of care therapies" are too toxic. A better approach is the use of continuous or more frequent low dose chemotherapy, known as metronomic low dose (MLD) chemotherapy, which is safer with a much longer duration of survival than standard cytotoxic chemotherapy and which provides a better quality of life for the elderly patient population.

Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is most prevalent in elderly patients, with a median age of 70 years at the time of diagnosis. To our knowledge, there are no trials designed to evaluate the safety and efficacy of treatment for elderly patients with PDAC. The standard of care for PDAC employs the "maximum tolerated doses" of multidrug chemotherapy regimens. These regimens require extended rest periods from chemotherapy, enabling the regrowth of tumor cells and permitting the cancer stem cells to repopulate, which results in acquired chemoresistance. In contrast, "metronomic chemotherapy" is the frequent administration of lower doses of chemotherapy, without extended rest periods, hypothesized to limit the mechanisms driving acquired chemoresistance. **Methods**: Here, we report on our clinical experience using various metronomic chemotherapy regimens for 115 patients. Patients were 65 years of age or older with Stage III or IV PDAC. The most frequently employed regimens included prolonged 14-21-day infusions of 5- fluorouracil given in conjunction with at least two additional drugs, including gemcitabine, nab-paclitaxel and/or cisplatin, often depending on chemosensitivity assays. **Results**: The median duration of treatment was 12 months (range 1-208 months). Ninety-three patients (81%) lived 12 months or longer with a median overall survival of 24.6 months (range 1- 240+ months). Eight patients achieved a complete response and forty patients had a partial response. The overall response rate was 42%. Thirteen patients are alive, eight of whom are in sustained remission. Survival rates generally showed an inverse relationship with age. Overall, the metronomic multidrug regimens were well tolerated; the most common Grade 3 or4 treatment related adverse events include neutropenia (14%), febrile neutropenia (1%), thrombocytopenia (17%), anemia (20%), anorexia (22%), fatigue (31%), vomiting (6%), diarrhea (13%), neuropathy (8%), stomatitis (12%), hypertension (17%), pulmonary fibrosis (8%), and hemolytic uremic syndrome (3%). There were two drug-related deaths, including one patient diagnosed with acute leukemia, and one patient who developed multiple liver abscesses and sepsis secondary to cholangitis. **Conclusions**: Taken together, these data indicate that the use of metronomic chemotherapy is associated with (1) improved overall response and remission rates (2) less systemic toxicity, (3) improved quality of life in elderly patients with pancreatic ductal adenocarcinoma, and therefore is a better approach for this population with PDAC.

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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is currently the third leading cause of cancer related death in the United States and is predicted to be the leading cause of cancer mortality by 2030 [1–3]. Within the past two decades, despite a better understanding of its biology and the development of innovative targeted and immunologic therapies along with the expanded availability of gene profiling, only modest progress has been made in prolonging survival. Its high mortality rate is in part the result of ineffective systemic therapies and the fact that the majority of patients are diagnosed with late-stage incurable disease [4].

PDAC usually affects older adults, with a median age of 70 years at the time of diagnosis, resulting in one of the most difficult therapeutic challenges [5]. Outcomes are typically worse than their younger counterparts due to age-associated comorbidities and poorer tolerance to standard chemotherapeutic intervention to date. There are no robust phase III clinical trials specifically designed for this subset of patients [6,7]. Compared to younger patients, the elderly not only have more chemotherapy-related toxicities but it is perceived that they derive fewer benefits from treatment. Quality of life, for many is frequently the focus, rather than survival [8].

Currently, the treatment of the elderly is usually based on data extrapolated from clinical trials in which this cohort of patients is not well represented. Trials are designed with strict exclusion criteria, limiting or eliminating older patients from participating. Even if age is not a criterion, selection processes for patients based on functional status and comorbidities unrelated to cancer contribute to poor recruitment [9,10]. Table 1 lists the ages, treatment drugs, number of patients, and survival reported inpublished studies on elderly patient with PDAC as compared to the data presented here by Isacoff et al.

Table 1. Comparison of Studies on Elderly Patients with PDAC.

Author	Age	Treatment	Number of Patients	Survival in Months (mOS)
Mizhi [11]	≥ 75	FOLFIRINOX	24	12.2
Kuroda [12]	≥ 65		519	6
Elias [13]	≥ 70	FOLFIRINOX	1972	6.8
		Gemcitabine & Abraxane		
		Gemcitabine		
	≥ 80	FOLFIRINOX	688	6.2
		Gemcitabine & Abraxane		
		Gemcitabine		
Jung [14]	≥ 70	FOLFIRINOX	36	9.2
		Gemcitabine & Abraxane		
		Gemcitabine		
Li [15]	≥ 70	FOLFIRINOX	30	10.6
		Gemcitabine & Abraxane		
		Gemcitabine		
McAndrew [16]	≥ 65	FOLFIRINOX	52	9.1
		Gemcitabine & Abraxane	21	7.7
		Gemcitabine		
			14	4.6
Isacoff	≥ 65		115	24.6

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The standard treatment for metastatic PDAC as recommended by guidelines established by the National Comprehensive Cancer Network (NCCN) is 5-Fluorouracil (5-FU), Leucovorin, Irinotecan, and Oxaliplatin (FOLFIRINOX) or Gemcitabine plus nanoparticle albumin-bound (nab)-Paclitaxel for patients with good performance status (ECOG 0-1) and who are less than or equal to 75 years of age [17]. The pivotal clinical trial which showed the superiority of FOLFIRINOX over Gemcitabine monotherapy chose to exclude patients older than 75 years [18]. Although FOLFIRINOX was associated with survival benefit over Gemcitabine, there were more adverse events, that included a higher incidence of grade 3 and 4 neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy as well as more episodes of febrile neutropenia. Similarly, in 2013, Von Hoff et al. reported an increase in survival rate for patients with PDAC who received nab-paclitaxel plus Gemcitabine compared to Gemcitabine alone [19]. Despite a slight survival benefit of 1.7 months observed in the Gemcitabine plus nab-Paclitaxel arm, the toxicity of this regimen was significant, including Grade 3 or higher neutropenia (38% in the nab-Paclitaxel–Gemcitabine group vs. 27% in the Gemcitabine group), fatigue (12% vs. 7%), neuropathy (17% vs. 1%), and febrile neutropenia (3% vs. 1%). Although the study did not have age as an exclusion criterion, only 10% of patients were over the age of 75.

Gemcitabine is recommended as monotherapy for elderly patients with poor performance status [17]. However, its benefit as a single agent is not unsupported by objective real-world data. For patients greater than 70, the median survival is only 4.5 months, and is associated with toxicity [13]. Some studies have shown that combination chemotherapy, albeit with dose reduction, is more beneficial for elderly patients over Gemcitabine monotherapy [20,21]. Because elderly patients with PDAC have been and continue to be underrepresented in clinical trials, the choice of the most effective and safe treatment is not well defined and represents an urgent unmet oncologic need. Approximately one-half of elderly patients choose not to be treated, in that they wish to avoid the toxic side effects of treatment so they can maintain a better quality of life [12].

Recently published data from some retrospective and small studies utilizing chemotherapy indicates that there is a benefit to elderly patients based on strict inclusion criteria that are primarily met by fit patients. The data indicate that outcomes are in many cases similar to younger patients. In general, the number of evaluated elderly patients are usually small with most patients receiving only one or two drugs and less than 20% receiving 3 drug combination therapy [5,13,22].

Elias et al recently reported that patients equal to or greater than 70 years of age who were treated with FOLFIRINOX, had a median survival of 9.6 months. This, however, represented less than 20% of eligible patients 70 years and older in their study [13]. Mizrahi et al reported the results of a retrospective analysis of modified FOLFIRINOX regimen in PDAC patients, age 75 or older at MD Anderson Cancer Center (MDA). Twenty-four patients were included. The median overall survival was 12.2 months. Forty-six percent of patients had Grade 3 or 4 hematological toxicities, 42% discontinued FOLFIRINOX due to toxicity, and 25% required hospitalizations. These 24 patients actually represent less than 10% of all elderly patients during the five and a half years of patient accrual [11].

Historically, regimens for PDAC have employed one, two, or three drugs at their maximum tolerated dose (MTD), believing that this “more is better” approach would kill more cancer, and therefore translate into a better outcome. Conventional MTD dosing is characterized as the administration of chemotherapeutic agents at their highest tolerated doses, followed by periods of rest. By contrast, low dose metronomic (LDM) dosing embraces the frequent or continuous administration of multiple drugs given at doses significantly lower than those currently recommended under standard of care, usually without prolonged breaks or rest periods [23]. It is associated with fewer dose limiting side effects, is more patient friendly, and has been shown to impart significant disease control in patients with various solid tumors [24–27].

There is now a growing body of scientific evidence that supports the use of LDM over MTD. These advances demonstrate that LDM suppresses tumor stem cell proliferation, activates the host immune response, inhibits tumor angiogenesis, and is associated with less drug-induced resistance and disease progression [28].

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In order to fully understand how LDM therapy works, it is important to first recognize that the focus of treatment is not directed toward highly proliferative cancer cells, but primarily at the tumor microenvironment (TME), which is a complex and dynamic ecosystem that is derived from and supported by the host [29].

The TME is composed of cells from mesenchymal, endothelial, and hematopoietic origin which make up the extracellular matrix (ECM), all of which interact with and control the behavior of tumor cells. The most dominant component within the TME is the cancer associated fibroblast (CAF), which when activated, secretes chemokines and cytokines, that play a critical role in the dynamic crosstalk between the many components within the TME [30]. Recent evidence reveals that MTD targets both the tumor and the host TME, causing damage to both. This results in the remodeling of the stroma which frequently promotes tumor progression and chemoresistance [31–33].

Cham et al demonstrated that metronomic dosing of Gemcitabine is active against pancreatic ductal adenocarcinoma. Dose reduction of more than 50% in the LDM treated patients resulted in significant tumor volume reduction when compared to MTD Gemcitabine regimen [34]. Metronomic Gemcitabine improved perfusion in tumors and reduced hypoxia without an increase in tumor cell proliferation. Improved vascular function resulted in better drug delivery during subsequent treatment cycles. They also observed that metronomic Gemcitabine induced marked decrease in proangiogenic growth factors and cytokines, and increased apoptosis of CAFs, suggesting that multiple stromal components were the targets of metronomic chemotherapy.

Hasnis et al studied metronomic Gemcitabine in mouse models bearing Human Panc-1 and murine Panc-02 pancreatic adenocarcinoma. Cohorts were treated with maximum tolerated dose (MTD) Gemcitabine and metronomic (MC) Gemcitabine. They showed that MTD Gemcitabine was pro-tumorigenic and it induced host pro-angiogenic and pro-metastatic effects which were mediated by host myeloid-derived suppressor cells (MDSCs). MDSCs become differentiated into macrophages and infiltrate the TME. This, in turn, results in increased proliferation and migration of endothelial cells (pro-angiogenic), increased pro-inflammatory cytokines, and a decrease in anti-inflammatory cytokines. Bone marrow derived proangiogenic endothelial progenitor cells were increased in the blood and TME after MTD chemotherapy which were felt to promote angiogenesis and accelerate metastasis as a result of the upregulation of growth factors and cytokines [35].

5-FU is approved for the palliative management of patients with pancreatic cancer. Low-dose continuous 5-FU infusion is more effective than bolus injections [36]. In a meta-analysis of 1219 cancer patients who received bolus versus infusional 5-FU, tumor responses and overall survival were significantly higher in patients treated with infusional versus bolus (22 vs. 14%) 5-FU. Hematologic grade 3 or 4 toxicities were less common with infusional 5-FU compared to bolus 5-FU. Ducreux et al. observed that there were higher response rates and significantly longer survival with the combination of infusional 5-FU and Oxaliplatin than with either infusional 5-FU or Oxaliplatin alone [37]. Further, addition of Irinotecan and Oxaliplatin to infusional 5-FU improved outcomes in the treatment of patients with pancreatic cancer compared to single-agent Gemcitabine [19].

Oral Capecitabine given at low doses is a potent angiogenic agent, and there is a synergistic effect when given with antiangiogenic agents. Recent work showed that withdrawal of antiangiogenic therapy resulted in a rapid rebound in neovascularization within tumors, causing tumor regrowth and potential acceleration of metastases. Long term maintenance therapy with an oral, low cost, antiangiogenic agent such as Capecitabine prevented tumor regrowth and progression [38,39].

In vitro, a synergistic effect on cell kill was seen when cells were exposed to Mitomycin C for 4 hours, followed by continuous exposure to 5-FU for 7 days [40].

On the basis of these preclinical findings, Isacoff et al. initially tested the efficacy of 5-FU administered as a protracted intravenous infusion in conjunction with Leucovorin (LV), dipyridamole, and Mitomycin C in advanced colorectal cancer [41]. There was 61% overall objective response with 10 complete responses. Subsequently, the same 4-drug combination was tested in locally advanced, non-metastatic pancreatic cancer. There was 39% overall response rate, a median

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overall survival of 15.5 months and a 1-year survival rate of 70% (n=15). Four patients underwent curative resection after being down-staged [42]. These results formed the basis for testing this rationally designed four-drug combination in a multi-institutional cooperative group setting (Southwest Oncology Group [SWOG] study S9700). In this study, patients with stage 2 and 3 PDAC had a median overall survival of 13.8 months and a 1-year survival rate of 54% [43].

More recently, Isacoff et al. combined low dose continuous 5-FU with Leucovorin, *nab*-Paclitaxel, Oxaliplatin, and Bevacizumab for patients with advanced PDAC. They observed an overall response rate of 49%, a median overall survival of 19 months with 82% of patients surviving 12 months or longer. They concluded that LDM chemotherapy combined with antiangiogenic targeted therapy was both safe and effective [44].

As previously stated, the majority of patients with PDAC are elderly and many have poor performance status. Metronomic regimens would be a better option in that they are more easily tolerated, safer, and are of equal or greater efficacy than MTD chemotherapy.

The purpose of this paper is to report on the efficacy and safety of combination chemotherapy using FDA approved drugs given on a metronomic schedule and dosing to patients 65 years of age or older in patients with advanced PDAC.

2. Materials and Methods

We retrospectively reviewed the charts of 115 patients with advanced PDAC who were 65 years of age or older. All patients were treated at The Pancreatic Cancer Center of Los Angeles between June 1, 2007 to July 30, 2024. The primary and secondary outcomes were median overall survival, the overall survival rate at one year, and the incidence of Grade 3 and 4 hematologic and non-hematologic toxicities. The median overall survival by age, the median duration of treatment and reasons for discontinuation of treatment were also analyzed.

2.1. Patients

Patients 65 years of age and older with stage III locally advanced unresectable or stage IV pancreatic ductal adenocarcinoma according to the American Joint Committee on Cancer (AJCC), and measurable disease were included in the retrospective analyses. Patients had Eastern Cooperative Oncology Group Performance Status of 0-2. All patients had at baseline, platelet count $\geq$100,000/mm^3, hemoglobin $\geq$ 9.0 g/dL, absolute neutrophil count $\geq$1500/mm^3, ALT/AST $\leq$2.5 times the upper limit of normal (ULN), total bilirubin $\leq$1.5 times the ULN, and creatinine $\leq$1.5 mg/dL. Treatment was not initiated until they were 2 weeks beyond a surgical bypass procedure or had recovered from surgery. Patients were excluded if they had a concurrent second malignancy or known history of current or previous central nervous system (CNS) metastatic disease. No patient was a candidate for curative surgical resection or radiotherapy.

2.2. Chemosensitivity Assay

Coded and deidentified samples were shipped at 4°C overnight to Adera Biolabs 9 (Germantown, MD, USA) for circulating tumor and invasive cell (CTIC) isolation and enriched as previously described [41]. Briefly, a collagen adhesion matrix in a modified cell invasion assay was used to capture epithelial cell adhesion molecules (EPCAMs) plus invasive cells, a well characterized approach for capturing circulating tumor cells (CTCs). The ChemoSensitivity Assay accurately measures the gene expression of 95 genes by quantitating mRNA levels by qPCR for each gene in circulating-tumor and invasive cells isolated from whole blood (6 mL). The seven chemotherapeutic agents modeled by the assay are Gemcitabine, nab-Paclitaxel, 5-FU, Oxaliplatin, Irinotecan, Mitomycin C, and Cisplatin [45].

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2.3. LDM Chemotherapy

Most patients were treated with Capecitabine or a prolonged IV infusion of 5-FU. Each was given in conjunction with 2 or 3 additional chemotherapeutic agents. The selection of which additional drugs to be utilized for each individual patient was based on the results of a chemosensitivity assay as previously described and by the physician discretion based on clinical judgment [14].

We utilized eight chemotherapeutic agents which were typically flat dosed as follows:

1. Gemcitabine 800 mg – 1000 mg IV over 30 minutes, weekly x3
2. nab – Paclitaxel 70 mg – 100 mg IV over 30 minutes, weekly x3
3. 5-FU 180 mg/m2 per day for 14 days via an ambulatory chemotherapy pump along with IV bolus Leucovorin
4. Capecitabine 1000 mg PO per day for 14 days
5. Oxaliplatin 60 mg – 80 mg IV over 120 minutes, weekly x3
6. Irinotecan 80 mg – 120 mg IV over 90 minutes, weekly x3
7. Mitomycin C 10 mg – 14 mg IV bolus, every 6 weeks
8. Bevacizumab 300 mg – 400 mg IV over 30 minutes, every 14 days

2.4. Frequently Used Regimens

The treatment intervention included infusional 5-FU/Leucovorin plus nab-Paclitaxel and Oxaliplatin as previously reported patients (n=44). Gemcitabine, nab-Paclitaxel, and Oxaliplatin (n=23), continuous 5-FU/Leucovorin, Irinotecan, and Oxaliplatin (n=13), continuous infusion of 5-FU/Leucovorin, Mitomycin C, and Bevacizumab (n=18), continuous infusion of 5-FU/Leucovorin, nab-Paclitaxel, and Gemcitabine (n=8), Gemcitabine, 5-FU, Leucovorin and Cisplatin (n=6), Capecitabine, Gemcitabine, and Oxaliplatin (n=3).

3. Results

A total of 115 patients were treated and evaluated. Baseline patient clinical characteristics are listed in Table 2. The median age was 74 (range: 65 – 92 years), with 55 being male and 60 female. Nineteen patients had Stage III disease. Forty-one patients had received prior therapy. The median duration of treatment was 12 months (range: 1 – 208 months). Treatment was discontinued because of disease progression (n=58), toxicity (n=25), patient and/or physician discretion (n=14), adverse events (n=4), allergy to Oxaliplatin (n=6), and patients moved to another location (n=8).

Table 2. Baseline Patient Clinical Characteristics.

Age (years)	
Median (range)	74 (65-92)
Sex	
Male	55
Female	60
ECOG Status	
0	50
1	44
2	21
Site of Primary Cancer	
Head	56
Body	34
Tail	25

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Surgery	
Yes	15
No	100
Previous Chemotherapy	
Yes	41
No	74
Extent of Disease	
III	19
IV	96
Site of Metastatic Disease	
Liver	54
Nodal	22
Lung	18
Peritoneal Carcinomatosis	22
Bone	2

3.1. Survival and Response

Ninety-three patients (81%) lived 12 months or longer. The median overall survival was 2.6 months, ranging from 1 – 240+ months. According to RECIST criteria on CT or magnetic resonance imaging (MRI) or pathologic assessment, eight (7%) patients achieved a complete response (CR rate of 7%) and forty (35%) patients achieved a partial response. Thirty-eight (33%) patients had stable disease. Taken together, this resulted in a disease control rate of 75% and overall response rate of 42%.

Thirteen patients are alive,11 of whom are in sustained remission and 2 of whom have active disease and continue on treatment. Of these living patients, 5 patients had locally advanced non-metastatic cancer, who received neoadjuvant chemotherapy and underwent surgical resection. These patients remain disease free from 4.3 to 18 years since diagnosis. Eight patients of the eleven who are in sustained remission, were treated for metastatic disease, 4 of whom had liver metastases and 4 with carcinomatosis..

3.2. Survival by Age

The median overall survival for all patients was 24.6 months, ranging from 1 – 240+ months. For the cohort of patients 65 – 70 years, the median overall survival was 28.4 months (range: 10 – 240+ months). For patients ages 71 - 80 years, the median overall survival was 21.7 months. For patients older than 80 years, the median overall survival was 15.8 months. Overall survival by age is listed in Table 3. We observed that with increasing age, there was a decrease in overall survival. Patients with Stage III had a longer median overall survival (40 months) than those with Stage IV disease (19 months).

Table 3. Overall survival time by age.

Overall Survival Time by Age	Patients (N)	mOS
All Patients	115	24.6 months
65 – 70 years	42	28.4 months
71 – 80 years	52	21.7 months
> 80 years	21	15.8 months

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3.3. Toxicity

The most common non-hematologic treatment-related grade 3 and 4 toxicities were fatigue (31%), anorexia (22%), stomatitis (12%), diarrhea (13%), and neuropathy (8%).

Nine patients developed pulmonary fibrosis as a result of either Mitomycin C or Oxaliplatin. Nineteen patients (17%) developed grade ≥ 3 hypertension, two of which were associated with hemolytic uremic syndrome.

Anemia was the most frequent grade 3 or 4 hematologic toxicity, seen in 23 (20%) patients. Grade 3 or 4 thrombocytopenia was observed in 20 patients (17%). There was one episode of febrile neutropenia. The most common grade 3 and 4 treatment related adverse events are listed in Table 4.

One patient was diagnosed with acute leukemia, from which he succumbed. One patient who developed multiple liver abscesses and sepsis secondary to cholangitis died while on therapy. These were the only drug related deaths. Eighteen patients (16%) were hospitalized.

Table 4. Most Common Grade 3 or 4 Treatment Related Adverse Events (N = 115).

Hematologic	**Number**	**Percentage**
Neutropenia	15	14
Febrile Neutropenia	1	1
Thrombocytopenia	20	17
Anemia	23	20
Non-Hematologic	**Number**	**Percentage**
Anorexia	25	22
Fatigue	36	31
Vomiting	7	6
Diarrhea	15	13
Neuropathy	9	8
Stomatitis	14	12
Hypertension	19	17
Pulmonary Fibrosis	9	8
HUS	3	3

4. Discussion

Pancreatic ductal adenocarcinoma is a disease that occurs primarily in the elderly, with a median age at diagnosis of 70 years. As the overall population continues to age, there will be a significant rise in the incidence of PDAC in the next decade. The management of elderly patients with PDAC will therefore gain increasing relevance and will need greater attention. Despite this relatively high incidence of PDAC in the elderly, there has been and continues to be a poor representation of this segment of the population in clinical trials. The management of older patients has been extrapolated from trials performed on younger patients. For the elderly, doses are modified and schedules changed which can impact outcomes.

In this paper, we retrospectively analyzed our experience in treating 115 elderly patients aged 65 or older with advanced inoperable pancreatic cancer. The majority of patients (85%) received a prolonged infusion of 5-FU with Leucovorin over a 14-day course or Capecitabine at metronomic doses and schedules. Each treatment was given in conjunction with at least two additional chemotherapeutic agents. We found that low-dose and frequently administered chemotherapeutic drugs were well tolerated and improved the overall survival of elderly patients with PDAC. The median overall survival of 24 months is twice as long as the 11 months reported in patients treated with FOLFIRINOX [19]. The observed 1 year of survival of 88% compares favorably to a 45% 1-year survival reported with FOLFIRINOX given to younger patients, who met strict inclusion criteria. Included in our study were many frail patients, 65 of whom had an ECOG score of greater than or equal to 1. In addition, there was no age restriction with the 21 patients who were over the age of 80.

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Multiple studies have recently reported on the management of the elderly with PDAC, showing that this cohort does benefit from treatment and may respond as well as their younger counterparts [14,16]. Of all available treatment options, that which has afforded the most benefit was FOLFIRINOX, achieving a median overall survival of 9-13 months in the same studies. These retrospective reviews showed that chemotherapy improves overall survival. However, for those patients who did receive treatment, it is frequently too toxic, poorly tolerated, and for the most part given for only 4 months or less. On the contrary, the patients in our retrospective analysis had fewer grade 3 & 4 adverse reactions. Sixteen percent of patients required hospitalization secondary to side effects or toxicity and fewer than 10% of patients received growth factors. The median duration of time on therapy was 12 months compared to the 4 months reported with Gemcitabine & Abraxane or FOLFIRINOX regimens [18, 19

The accepted paradigm for treating pancreatic cancer employs administration of a few drugs at or near the maximum tolerated dose (MTD) followed by drug-free intervals. Skipper et al observed that the more you give, the more you kill (dose-response) is valid only for non-mutagenic cells growing in log-phase [46]. Cancers in adult patients, do not grow logarithmically, and their cancers are highly mutagenic. This model does not work in clinical practice [47]. Despite these concerns, the oncologic community has for five decades embraced the concept of dose-response cell kill. MTD has thus far, for the vast majority of elderly patients, proven to be unsafe and only marginally effective for patients with PDAC, as observed in the real-world experience.

It is now widely accepted that the tumor microenvironment (TME) is responsible for cancer initiation, progression, resistance, and metastasis. The TME or stroma is a dynamic multicellular ecosystem that is composed of cells from mesenchymal, endothelial, and hematopoietic origin which make up the extracellular matrix (ECM), all of which interact with and control the behavior of tumor cells.

Metronomic chemotherapy is antiangiogenic by its ability to target tumor associated endothelial cells in the TME. These cells communicate with tumor cells and other stromal elements via the release of angiocrine factors that control tumor growth and metastasis. Tumor associated endothelial cells are extremely sensitive to continuous low-dose treatment, which reduces their proliferation and impairs vessel formation. The suppression of pro-angiogenic factors, like vascular endothelial growth factor (VEGF), and the upregulation of antiangiogenic mediators such as thrombospondin-1 (TSP1) results in reduced metastatic potential [48–50].

Browder et al developed an anti-angiogenic dose schedule for the administration of Cyclophosphamide. In resistant cell lines, the anti-angiogenic schedule suppressed tumor growth more effectively than the conventional dosing schedules. All anti-angiogenic schedules of Cyclophosphamide induced apoptosis of endothelial cells and observed apoptosis of drug-resistant tumor cells. Anti-angiogenic effects have been demonstrated in vitro for 5-Fluorouracil and Mitomycin C as well. At low dose schedules in vivo, anti-angiogenic effects have been shown for MTD Vincristine, Vinblastine, Doxorubicin, Paclitaxel, and Etoposide [51].

Many studies have shown that LDM therapy in vitro and in vivo induces apoptosis of endothelial cells within the tumor vascular bed by upregulation of the endogenous angiogenesis inhibitor TSP-1. It is also established that MTD reduces the expression of TSP-1, and that this downregulation has a positive effect on endothelial survival [52].

During periods of breaks between cycles of MTD chemotherapy, there is marked mobilization of hematopoietic progenitors from the marrow into the peripheral blood, which is a known response to the chemotherapy induced myelosuppression. Bertolini et al showed that the administration of Cyclophosphamide at MTD versus frequent LDM have opposite effects on the mobilization of circulating endothelial progenitor (CEPs) in tumor bearing mice. They concluded that, in addition to the anti-angiogenic mechanisms in which fully differentiated endothelial cells are killed by LDM chemotherapy, an anti-vasculogenic process is also involved, which is mediated through its ability to reduce circulating CEP that rebound after MTD chemotherapy [53].

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Another advantage of LDM chemotherapy is that it is effective in enhancing the host's immune response compared to MTD chemotherapy. While the recognition of tumor associated antigens is necessary for adaptive anti-tumor immunity, other factors, such as damage associated molecular patterns are critical in boosting adjuvanticity, which describes the process by which antigen presenting cells (APCs) are recruited and activated [54]. LDM Gemcitabine for instance, was demonstrated to increase MICA/B protein expression on pancreatic cell lines [55]. Mitomycin C, despite synergy with 5-Fluorouracil, has several mechanisms of pro-immunogenic activities [56]. For example, via increased permeability of the mitochondrial membrane, Mitomycin C leads to dendritic cell activation [57]. In vitro data suggest that Mitomycin C may facilitate tumor antigen presentation to T cells via CD40, CD86, and CD80 secretion as well as increased expression of Major histocompatibility complex (MHC) class II proteins [58]. Paclitaxel and Cisplatin may also stimulate cytotoxic T cell activity via the increased permeability of granzyme B [59]. Not only does LDM chemotherapy upregulate anti-tumor immune effectors, low-dose Gemcitabine, for example, has been shown to cause a decrease in myeloid derived stem cells, which have been shown to hinder anti-tumor immunogenicity to dendritic cells [60].

In addition to preventing pro-tumorigenic angiogenesis and increasing the immunogenic recognition of tumor antigens, LDM chemotherapy may have particular effects on cancer stem cells, potentially preventing tumor recurrence/persistence. LDM chemotherapy, for example, was shown in pancreatic tumor xenografts to have fewer cancer stem cells, while MTD chemotherapy was shown in another study to stimulate the conversion of cancer cells into those resembling cancer stem cells [61]. Tumor resistance, with LDM Cisplatin, was reduced and demonstrated superior efficacy as well, against tumor resistant non small cell lung cancer (NSCLC) cell lines as compared to MTD Cisplatin [62]. The antitumor effects of Cisplatin were shown to be significantly more beneficial on a metronomic dosing schedule when compared to MTD dosing.

A number of studies have demonstrated that LDM chemotherapy decreased proliferation of and survival of cancer stem cells [63,64]. In vitro, LDM Paclitaxel reduced the cancer stem cell population. Vive et al. showed that LDM Cyclophosphamide depleted the cancer stem cell population in a xenograft model of pancreatic cancer. Chan et al showed that in MTD – Doxorubicin treated tumor bearing mice, the cancer stem cell population substantially increased but not in the LDM – Doxorubicin treated mice. They concluded that LDM – chemotherapy treatment most likely reduced activation of cancer associated fibroblasts, reduced chemokine production and, consequently, decreased the cancer stem cell expansion.

Cancer stem cells play a critical role in cancer resistance. They are highly resistant to conventional chemotherapy. The critical pathway of cancer stem cells which is essential for self-renewal, are the epithelial to mesenchymal transition (EMT) process which is in part responsible for resistance to conventional therapy. Cancer stem cells are, as well, universally resistant to most treatments that prevent the complete eradication of the tumor, because of its quiescence.

Our study has limitations. The retrospective design and single-arm nature preclude definitive conclusions regarding efficacy and safety. Moreover, while our comparisons to published outcomes in elderly cohorts receiving standard therapy are informative, prospective randomized trials are necessary to validate the clinical benefit of metronomic chemotherapy in this setting. Future studies should also explore biomarkers of response and resistance, as well as the integration of metronomic chemotherapy with other therapeutic modalities, such as immune checkpoint inhibitors or stroma-targeting agents.

5. Conclusions

In conclusion, metronomic chemotherapy appears to be a tolerable and potentially effective treatment strategy for elderly patients with advanced pancreatic ductal adenocarcinoma regardless of age or performance status. Its multiple mechanisms of action—ranging from antiangiogenic and immunomodulatory to anti-cancer stem cell activity—offer a compelling biological rationale for continued investigation, particularly in a patient population for whom conventional therapy is often

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inappropriate and unsafe. Hence, metronomic chemotherapy for elderly patients with pancreatic ductal adenocarcinoma would be a better treatment approach.

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Abbreviations

The following abbreviations are used in this manuscript:

PDAC	Pancreatic ductal adenocarcinoma
mOS	median overall survival
NCCN	National Comprehensive Cancer Network
ECOG	Eastern Cooperative Oncology Group
5-FU	5-fluorouracil
LV	Leucovorin
FOLFIRINOX	5-FU, Leucovorin, Irinotecan, Oxaliplatin
nab	nanoparticle albumin-bound
AJCC	American Joint Committee on Cancer
PCTC	Pancreatic Cancer Treatment Center
ULN	upper limit of normal
CNS	central nervous system
RECIST	Response Evaluation Criteria in Solid Tumors
CR	complete response
PR	partial response
LDM	low-dose metronomic
MTD	maximum tolerated dose
TME	tumor microenvironment
ECM	extracellular matrix
CAF	cancer-associated fibroblast
CTIC	circulating tumor and invasive cell
EPCAM	epithelial cell adhesion molecule
CTC	circulating tumor cell
qPCR	quantitative polymerase chain reaction
G-FLIP	Gemcitabine, 5-FU/Leucovorin, Irinotecan, and Platinum

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