ORIGINAL ARTICLE

Long-Term Outcomes of the Treatment of Unresectable (StageIII- IV) Ductal Pancreatic Adenocarcinoma Using Metabolically Supported Chemotherapy (MSCT): A Retrospective Study

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ABSTRACT

Introduction Metabolically supported chemotherapy, is defined as the application of standard chemotherapy protocols concomitant to the administration of pharmacological doses of regular insulin and the development of hypoglycemia, and following fasting starting the previous day. This study aims to present the effects of metabolically supported chemotherapy on the overall survival of locally advanced and metastatic (stage III and stage IV, respectively), or simply unresectable pancreatic adenocarcinoma patients. **Material and methods** This study is a retrospective analysis of a prospectively maintained database of patients. It includes all patients that applied to our clinic between July 2012 and December 2014 that were diagnosed with unresectable (stage III-IV) pancreatic adenocarcinoma. The demographic data of all the patients as well as the chemotherapy regimen received, date of treatment initiation, date of disease remission, mortality and overall survival of all patients were analyzed using SPSS 20.0. Patient follow-up was performed by means of computed tomography and positron emission tomography–computed tomography scans. **Results** 33 patients, 24(73%) males and 9(27%) females, were included in our study. The majority, 27(81%) patients, had metastatic disease at the time of diagnosis and were stage IV. While 11(33%) of the patients were treated using a gemcitabine-based protocol, 13(39%) received FOLFIRINOX. 9(27%) of the patients were initially treated using gemcitabine, but began receiving FOLFIRINOX following progression as second-line chemotherapy. Statistical analysis revealed a median survival of 19.5 months and a 1-year survival rate of 82.5%. Presently, 18(54%) of the patients remain healthy and alive, free of disease progression with eastern cooperative oncology group performance statuses ranging between Grade 0 -1. 4(22%) of these patients ultimately underwent radical pancreatic surgery: 3(17%) having undergone pancreaticoduodenectomies (Whipple procedures) and 1(5%) having undergone a distal pancreatectomy. **Conclusion** This study demonstrates that a metabolically supported form of applying standard chemotherapy regimens may enhance the overall survival rates of unresectable (stage III-IV) pancreatic adenocarcinoma patients.

INTRODUCTION

Ductal pancreatic adenocarcinoma is currently the most aggressive, invasive and fatal of all solid malignancies [1]. Accounting for approximately 85% of all pancreatic neoplasms, it is also the most common histological type of pancreatic tumors [2]. Radical surgery is currently the only form of curative treatment. However, only 15% to 20% of patients have resectable disease at initial presentation [1, 3]. Because there are no early detection tests and because pancreatic adenocarcinoma does not present with symptoms early on, the majority of patients are usually diagnosed only after the disease has become locally advanced (stage III) – encasing neighboring major blood vessels passing close to the pancreas, such as the celiac axis or the superior mesenteric artery - or after it has metastasized to other parts of the body (stage IV), in both

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cases becoming unresectable. In patients not suitable for resection with curative intent, palliative chemotherapy is usually employed for prolongation of survival and control of tumor growth.

In 1924, when Otto Warburg recognized that, unlike normally differentiated cells, cancer cells carry out glycolysis instead of oxidative phosphorylation for energy generation [4], research regarding a metabolic approach to cancer treatment began. This research ultimately led to the development of Metabolically Supported Chemotherapy (MSCT), a method based on Warburg's hypothesis that "cancer is a disease of metabolic dysregulation" [5]. Centered on various types of metabolic adjustments directed towards correcting metabolic dysregulation on a cellular level, MSCT involves the administration of pharmacological doses of regular insulin and the development of hypoglycemia, and is applied following fasting starting the previous day [6, 7]. While standard chemotherapy for patients with locally advanced and metastatic disease has been gemcitabine-based regimens until recently, because it confers a significant improvement in the overall survival of these patients, FOLFIRINOX is also considered as a therapeutic option. The present study is a descriptive, retrospective study that aims to evaluate and report the response of unresectable, or locally advanced and metastatic patients to MSCT.

MATERIAL AND METHODS

The medical records of all 38 patients that applied to our clinic between July 2012 and December 2014, that were diagnosed with locally advanced (stage III) or metastatic (stage IV), or in other words, unresectable pancreatic adenocarcinoma were retrospectively analyzed using a prospectively maintained database. 5 patients eventually had to be excluded from the analysis: 4 because they refused treatment (due to costs, etc.) without ever having received MSCT and 1 patient because he died due to a pulmonary embolism after having received 2 doses of MSCT and before having undergone a follow-up PET-CT or tumor marker analysis, which would allow for an objective evaluation of response to MSCT. The age, gender, date of diagnosis, presence of locally advanced unresetable or metastatic disease, chemotherapy regimen (gemcitabine-based protocol or FOLFIRINOX) administered, date of treatment initiation, date of disease remission, mortality, cause of death and overall survival of the remaining 33 patients were evaluated and statistical analyses were performed using original SPSS 20.0 software (IBM Corp, NY, USA). Survival curves were estimated using the Kaplan-Meier method and patients alive were censored at the time of their last follow-up consultation. All patients that were included in the present study received either a standard gemcitabine-based chemotherapy regimen, also including cisplatin and 5-fluorouracil (5-FU) or the FOLFIRINOX regimen, a combination of folinic acid, fluorouracil, irinotecan and oxaliplatin, during the initial 3-month period of their treatment. With the patients' written, informed consent and following a fast starting the previous night, regular insulin (Humulin® R) in doses ranging between 5-20 IU were administered prior to each chemotherapy session. When a hypoglycemia state with blood glucose levels around 50-60 mg/dl for normoglycemic patients were achieved, chemotherapy delivery was initiated. All chemotherapy agents were administered at standard doses, these being 1000 mg/m^2 for gemcitabine, 30 mg/m^2 for cisplatin, 400 mg/m^2 for fluorouracil in the case of the gemcitabine-based chemotherapy regimen and 400 mg/m^2, 400 mg/m^2, 180 mg/m^2 and 85 mg/m^2 for fluorouracil, folinic acid, irinotecan and oxaliplatin, respectively, in the case of the FOLFIRINOX regimen. The FOLFIRINOX chemotherapy regimen was later followed by a 46-hour continuous infusion of 5-FU at a dose of 2400 mg/m^2 [8]. The gemcitabine-based regimen was administered on days 1 and 8 of a 21-day cycle and the FOLFIRINOX chemotherapy regimen administered on days 1 and 15 of a 28-day cycle. Insulin delivery and chemotherapy infusions were always done in conjunction with blood glucose monitoring. These cycles were repeated for a total of 3 months and were eventually followed by a treatment response evaluation. Patients' responses to treatment (regression vs. progression of disease) were assessed by means of serum tumor marker level analyses (CEA and CA 19-9) as well as PET/CT imaging performed every 3 months throughout the treatment period until complete metabolic response was achieved and FDG uptake was no-longer detected. Follow-up evaluations for those patients with complete response were carried- out by means of serum tumor marker level analyses (CEA and CA 19-9) and CT imaging using contrast material every 3 months following the achievement of complete response. While patients that achieved regression based on their CT or PET-CT results proceeded with the same regimen started initially for an additional 3 months as maintenance therapy, patients that demonstrated disease progression began receiving FOLFIRINOX (if they initially were receiving a gemcitabine-based chemotherapy regimen) or proceeded with dose adjustments.

RESULTS

33 patients were included in our study, 24(73%) of these patients being males and 9(27%) being females. The mean age of these patients was 61 (±20, range: 41-81) years and the majority, 27(81%) patients, had metastatic disease (stage IV) at the time of diagnosis. While 11(33%) of the patients were treated using a gemcitabine-based protocol, 13(39%) received FOLFIRINOX. 9(27%) of the patients, on the other hand, were initially treated using gemcitabine, but began receiving FOLFIRINOX following disease progression as second-line chemotherapy **Table 1**. Median follow-up time for patients included in the present study was 13.79 months (min-max: 5.49-58.45). Statistical analysis of the patients' data revealed a median survival of 19.483 (±3.541 SE, 95% CI, 12.541 to 26.424) months (range: 5.5-58.4), a mean survival of 27.352 (± 4.578 SE, 95% CI, 18.378 to 36.326) and a 1-year survival

rate of 82.5% (±7.2 SE). Median and mean progression-free survival were determined as being 6.396 (± 1.006 SE, 95% CI, 4.424 to 8.367) months and 4.6 (±0.34 SE, 95% CI, 3.934 to 5.265) months, respectively **Table 2**. No significant difference was detected between the overall survival rates and progression-free survival rates of patients that received MSCT in the form of the gemcitabine-based regimen and those of patients that received MSCT in the form of FOLFIRINOX. While analyses revealed disease progression as the most common cause of mortality among those patients that died, the cause of death in the case of 47% of the patients that died was unrelated to pancreatic adenocarcinoma and included such causes as, intestinal obstruction, hepatic cirrhosis and neutropenia. Finally, it should be noted that, presently, 18(54%) of the patients included in this study remain healthy, alive, and free of disease progression with ECOG performance statuses ranging between Grade 0-1 **Figure 1**.

All patients that are currently alive have achieved complete response. In addition, all of these patients have been referred to general surgeons for evaluation for radical pancreatic surgery (Whipple or distal pancreatectomy), as surgery remains as the only reported "cure" for pancreatic cancer. 3(17%) of the 18 patients underwent pancreaticoduodenectomies (Whipple procedures) following the achievement of complete response with MSCT. 1(5%) underwent a distal pancreatectomy. All 4(22%) patients are among the 18 patients that remain alive. The remaining patients that are currently alive were not operated on, as surgeons deemed the continuation of maintenance MSCT a better option for these patients.

Table 1. Patients' demographic, treatment, surgery and survival status details.

Characteristics	Variable	No (%)
Number of patients	Total sum	33
Age (yrs)	Mean (±20, range: 41-81)	61
Sex	F	9 (27)
	M	24 (73)
Disease / tumor location	Metastatic disease	27 (81)
	Locally advanced disease	6 (19)
Treatment protocol	Gemcitabine	11 (33)
	FOLFIRINOX	13 (39)
	Gemcitabine followed by FOLFIRINOX	9 (27)
Survival status	Alive	18 (54)
	Dead	15 (46)
Radical pancreatic surgery status (among alive)	Whipple procedure	3(17)
	Distal pancreatectomy	1(5)

Table 2. Survival times of the 33 patients evaluated in the present study.

Survival time (months)	Range (min – max)	n=33, No (%)
05-10	50.5 - 10.8	9 (27)
11-15	11.1 - 15.8	12 (36)
16 - 20	17.6 - 20.2	4 (12)
21 - 25	21.2 - 25.3	5 (15)
26 - 30	27.4	1 (3)
31 - 55	57.5 - 58.4	2 (6)

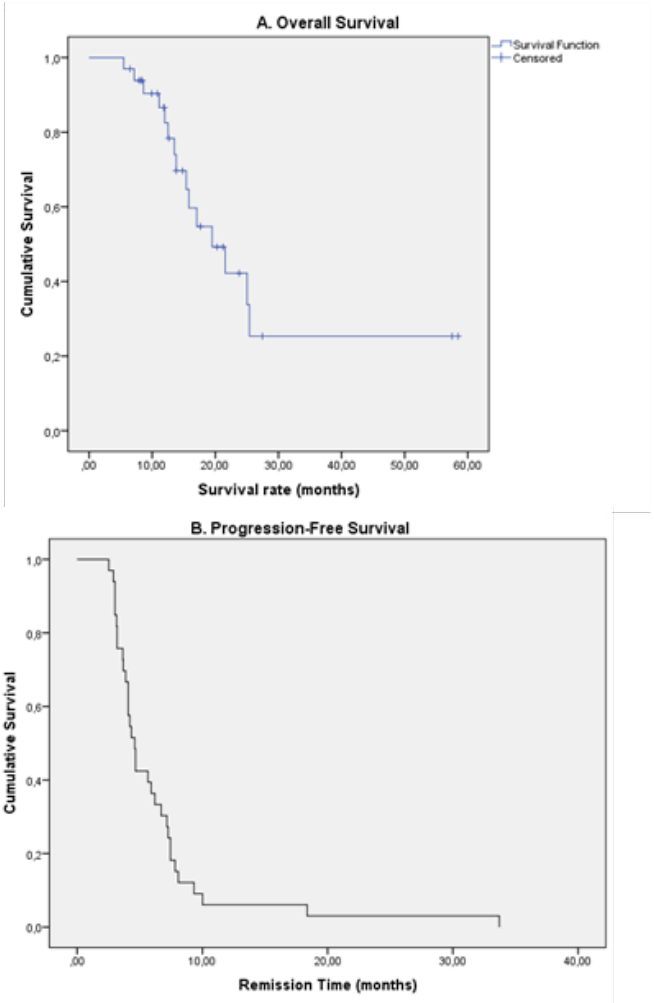

Figure 1. Kaplan-Meier Curves for Overall Survival (Panel a.) and Progression-Free Survival (Panel b.) of 33 patients included in the present study.

DISCUSSION

Along with lung cancer, over the last three decades pancreatic cancer has shown the least improvement in survival rates of all common cancers [9]. Globally, ductal pancreatic adenocarcinoma is the fourth most common cause of deaths due to cancer among both men and women [10] and despite decades of research, it continues to have a very dismal prognosis. Even though the survival rates improved from 2% in cases diagnosed in 1975-77, and 4% in 1987-89 diagnoses, at present the five-year survival rate of pancreatic adenocarcinoma still remains at only ~5% [11] and, even in the setting of completely resected node-negative pancreatic cancer, almost all patients are expected to die from this disease [12]. Numerous recent trials comparing different chemotherapy regimens employed in the treatment of metastatic and locally advanced unresectable pancreatic adenocarcinoma have reported improved survival rates. Nevertheless, no treatment protocol has been able to achieve a survival rate above one year [2, 13].

In patients with locally advanced or metastatic tumors not suitable for curative surgery, gemcitabine (GEM) treatment in conventional dosing (1000 mg/m^2 over 30 min) was the standard chemotherapy until recently [14,

15]. Nonetheless, in trials conducted more recently, the FOLFIRINOX chemotherapy regimen was found to be more effective than gemcitabine alone [8]. FOLFIRINOX also apparently delayed deterioration of quality of life [3]. At present, there is no standard chemotherapy regimen for patients with refractory disease, or patients that demonstrate disease progression following first-line treatment and according to the results of one United States cooperative group trial (CALGB #80303), fewer than half of patients with advanced pancreatic cancer proceeded to receive any additional therapy after progressing on first-line treatment [16]. This is mostly because most patients are unable to withstand further treatment following first-line chemotherapy. A small clinical trial recommends 5-FU combined with oxaliplatin, reporting an added benefit subsequent to first-line gemcitabine [17]. First line FOLFIRINOX, on the other hand, can be followed by gemcitabine in the case of patients with an adequate performance status [18]. Capacitabine, as a single agent or combined with oxaliplatin (referred to as CAPOX or XELOX), can also be considered as an option for second-line treatment [1].

The patients included in the present study received standard chemotherapy regimens, either a gemcitabine-based protocol or FOLFIRINOX, throughout the time they were treated using MSCT. FOLFIRINOX was the regimen of choice in the case of refractory disease for those patients that received a gemcitabine-based chemotherapy as first line treatment. Those patients, who had refractory disease despite FOLFIRINOX, were managed by way of dose adjustments. What separates the patients included in the present study from those patients that receive standard chemotherapy-alone are two metabolic adjustments: fasting starting from the evening of the previous day and the administration of regular insulin prior to their chemotherapy infusions and, therefore, the induction of hypoglycemia. Insulin was administered at pharmacological doses and only in order to achieve metabolic regulation and mild hypoglycemia (50-60 mg/dl). Nevertheless, based on the results of our study it is possible to state that the simple integration of insulin and induction of mild hypoglycemia prior to treatment protocols ultimately has a very significant impact on the survival of unresectable (stage III - IV) pancreatic cancer patients. Earlier studies report a median survival of 2.5 months for advanced stage pancreatic cancer patients only given best supportive care [19]. Although its benefit appears limited, chemotherapy improves this survival rate to some extent: it is reported that while a gemcitabine-based treatment provides a median survival rate of 6.2 months, a median progression-free survival rate of 3.3 months and a 1-year survival rate of 20% [8, 20], FOLFIRINOX confers a median survival rate of 11.1 months, a median progression-free survival rate of 6.4 months and a 1-year survival rate of 48.4% [8]. Overall, reports state that the chemotherapy regimens employed in treating pancreatic adenocarcinoma regardless of disease stage are associated with overall survival rates between 4-8 months median and progression-free survival rates in the range of 2-4 months [21]. In contrast to these survival rates, the present study demonstrates that MSCT can allow for a median survival of 19.5 (range: 5.5-58.4) months, a median progression-free survival rate of 6.4 months and a 1-year survival rate of 82.5% **(Table 3)**. It is important to note that, similar to the prior mentioned studies reporting the survival rates provided by standard chemotherapy, this study exclusively evaluated the treatment results of patients suffering from advanced stage pancreatic cancer. Regardless, however, the survival rates of those patients evaluated in this study are nearly twofold the highest survival rates reported previously for standard gemcitabine-based chemotherapy and for FOLFIRINOX. In addition, these survival rates are neither final nor definitive, as 54% of the patients included in this study remain alive and disease-free. Finally, it is also significant to note that, as a study reporting the findings of patients suffering from unresectable pancreatic adenocarcinoma, this study includes patients diagnosed with both stage III and stage IV disease. However, no separate analysis of these two groups was made in this study. A separate analysis for these two groups is not necessary because, at this stage of disease, guidelines recommend the same treatment protocols (i.e. gemcitabine-based chemotherapy or FOLFIRINOX) with similar survival rates. Contemporary trials evaluating different chemotherapy combinations in mixed populations of patients with locally advanced and metastatic pancreatic cancer suggest that the impact of chemotherapy on survival among patients with locally advanced and metastatic disease may be of approximately of the same magnitude [22, 23].

It should be stated that, although further research and statistical analyses are necessary in order to make an objective statement, our observation has been that, in comparison to those patients receiving standard chemotherapy, the patients included in the present study and, therefore, treated using MSCT suffered from less toxicity and experienced fewer side effects (including hair loss, nausea, diarrhea, vomiting, neutropenia, etc.). Overall, they were able to perform normal daily activities throughout the period they were receiving treatment throughout the period they were receiving treatment with ECOG performance statuses ranging between Grade 0-1. No problems were encountered due to fasting and/or hypoglycemia.

Table 3. Comparison of the treatment results of standard gemcitabine-based treatment, FOLFIRINOX and MSCT (metabolically supported chemotherapy).

	Gemcitabine (*)	FOLFIRINOX (**)	MSCT
Median survival rate	6.2 months	11.1 months	19.5 months
1-year survival rate	20%	48.40%	82.50%

(*) Sultana A, Smith CT, Cumnnigham D, *et al.* Meta-analyses of chemotherapy for locally advanced or metastatic pancreatic cancer. J Clin Oncol 2007; 25:2607-2615.
(**) Conroy T, Desseigne F, Ychou M, *et al*. FOLFIRINOX versus gemçstabine for metastatic pancreatic cancer. N Engl J Med 2011; 364:1817-1825.

Research shows that insulin, together with insulin-like growth factors I and II (IGFs), is central to the malignant metabolism of cancer cells [7] and the mechanism through which insulin enhances the efficacy of chemotherapeutics and allows for less toxicity and a better quality of life has been researched extensively. Studies demonstrate that insulin enhances the cytotoxic effects of chemotherapeutic drugs, first of all, by increasing membrane fluidity and permeability, therefore, allowing for increased drug penetration [6, 24, 25, 26]. The adsorption of drug molecules onto insulin and the formation of drug-insulin complexes, later internalized by receptor-mediated endocytosis, have also been discussed as causes for increased intracellular drug levels and resulting increased cytotoxicity [27, 28, 29, 30]. The metabolic modification that insulin brings about in cancer cells is, perhaps most importantly, related to the cross reaction of insulin with IGF receptors located on cancer cell membranes. In contrast to normal cells, cancer cells have an increased number of insulin and IGF receptors on their cell membranes (For example, breast cancer cells have approximately seven times more insulin receptors [31] and ten times more IGF receptors [32] in comparison to the cell membranes of healthy cells). This cross-reaction between insulin and IGF receptors extends the S-phase fraction of the cell cycle [33] and ultimately renders cancer cells more susceptible to the cytotoxic effects of anticancer drugs, especially in the case of cell-cycle phase-specific agents [34]. All in all, as this study demonstrates, adding insulin to chemotherapy regimens allows for increased efficacy – as actually higher intracellular doses are achieved within cancer cells –and an increased level of safety – as the lower concentration of insulin receptors on normal cells relatively spares them from the intensity of the cytotoxic effects of chemotherapeutic drugs [35].

This study is the first study discussing MSCT and its application in the treatment of unresectable (stage III-IV) pancreatic adenocarcinoma. It is limited in that its analyses only include patients that received MSCT. It does not include a group of patients that received standard chemotherapy in its evaluation. Nevertheless, although further research is necessary to support this innovative approach to cancer treatment, based on the survival rates of the patients included in the present study, MSCT appears to significantly improve the long-term outcomes of patients with locally advanced and metastatic pancreatic adenocarcinoma. The standardization of this method of chemotherapy delivery is important, as it may improve the survival rates of thousands of patients suffering from metastatic and locally advanced unresectable pancreatic adenocarcinoma unresectable pancreatic adenocarcinoma worlwide.

CONCLUSION

This study demonstrates that a metabolically supported form of applying standard gemcitabine-based chemotherapy regimens and FOLFIRINOX may enhance the overall survival rates of unresectable (stage III-IV) pancreatic adenocarcinoma patients.

Conflict of Interest

The authors declare that they have no conflicts of interest

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