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Metabolic Therapy of Pancreatic Cancer

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Abstract

Pancreatic cancer mortality rates are the highest and most predictable ones. This pathology is considered to be uniformly fatal regardless of therapeutic approach. According to international data bases and several meta-analyses, the survival at one-year from diagnosis stands at 5% in European, Australian and New Zealand studies and at 29% in American studies, which include endocrine pancreatic cancer. Average survival time ranges from 4 to 6 months. For 98% of cases showing metastasis at the time of diagnosis, death occurs within six months.

A metabolic treatment based on the nutri-pharmacological blockade of aerobic glycolysis (Warburg effect), and glutaminolysis, by means of a competitive inhibition of the rate limiting enzymes hexoquinase-2 (HK2), Lactate Dehydrogenase (LDHA) and Glutaminase (GS) through structural analogs of their physiological substrates, in the context of total blood glucose deprivation (Nuliglycaemia lucidae), seems to significantly prolong survival. This study describes the impact of the above-mentioned metabolic approach –as the sole form of therapy– on the one year survival rate and overall survival of 22 patients.

Keywords: Pancreatic cancer; Metabolic therapy; Competitive inhibition; Structural analogs

Introduction

Pancreatic cancer is considered one of the most lethal forms of neoplasm, with a mortality/incidence rate nearing 98% [1,2]. According to the American Cancer Society and the GLOBOCAN data base, managed by the International Association of Cancer Registries (http://globocan.iarc.fr), pancreatic cancer morbidity is increasing. In industrialized and developing countries, regardless of their ethnic group, the Age-Standardized Rate (ASR) fluctuates between 4.9 and 7.6 per 100,000 men and between 3.6 and 4.9 per 100,000 women, whilst the mortality rate closely follows those same figures. The uniformity of this phenomenon is validated by epidemiological data reported by culturally and ethnically different nations such as China [3], England/Wales [4], and Mediterranean countries [5], with an overall survival at around 4.1 months after diagnosis, and a one-year survival rate as low as 2.21% [6]. Usually relevant factors in the therapeutic outcome of other oncological pathologies -such as clinical presentation or the waiting period between diagnosis and beginning of treatment- do not improve prognosis in exocrine pancreatic cancer cases [7]. Standard pancreatic cancer therapies consist in primary surgery (total or partial pancreatectomy, Whipple procedure –partial pancreaticoduodenectomy-, stent placement in the bile duct and/or chemotherapy and radiotherapy) [8]. Attempts to prolong survival by means of more aggressive surgery, in addition to some common procedures (such as the extended lymphadenectomy), not only fail to prolong life, but generally aggravate clinical condition [9].

CISA Metabolic Approach Protocol

The CISA (Competitive Inhibition with Structural Analogs) method for the treatment of solid tumors has been previously described at length elsewhere [10]. Succinctly, the procedure consists of consecutive intravenous injections of structural analogs of glucose and glutamine [2-Deoxi-D-Glucose ($C_6H_{12}O_5$), glucosamine ($C_6H_{13}N_1O_5$), sodium ascorbate ($C_6H_7NaO_6$)] under deep physiological ketosis, induced by means of a restricted ketogenic diet. Physiological ketosis, defined as: ketonemia ≥ 2 mM/L and glycemia ≤ 4.5 mM/L (or any other combination where the Ketonemia/Glycaemia quotient is equal to or higher than 0.4), essentially differs from diabetic ketosis, which is characterized by sustained hyperglycemia in a range of 14 to 25 mM/L and pH <7.25. Additional interventions, such as intravenous insulin injections (15 to 80 IU, bolus), further depress glucose plasma concentration into single digit levels, thus favoring competitive inhibition by the above-described chemical analogs, which bear structural affinity with, but lack the intrinsic

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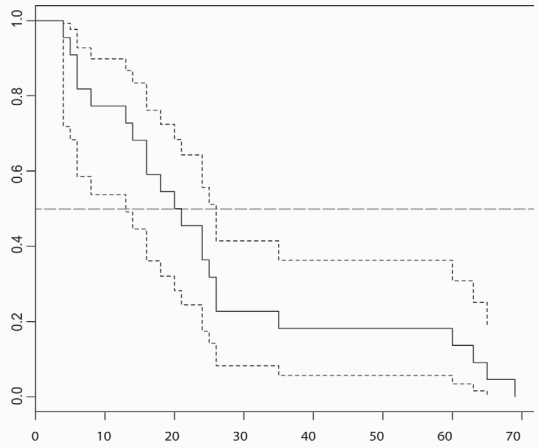
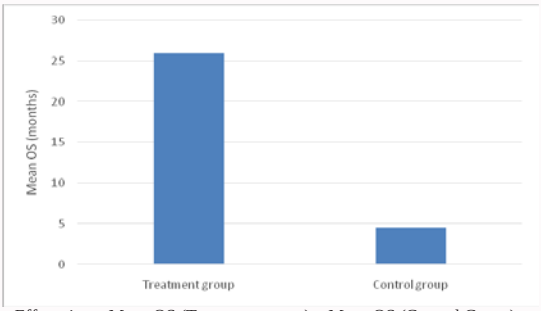


Figure 1: Overall survival of the treatment group (months).



Effect size = Mean OS (Treatment group) − Mean OS (Control Group) / Standard Deviation

Effect size = 26-4.5 / 19 = 1.13

Figure 2: Comparative mean OS of treatment and control groups. Calculation of effect size.

activity of natural substrates. The purpose of the CISA protocol is to induce an energy crisis in pathologically hyper metabolic tissues. To that end, each treatment cycle consists of 35 intravenous injections of the appropriate combination of the above-described enzymatic inhibitors.

This approach exploits the Warburg effect, the paradoxical increase of fermentative glycolysis of neoplastic cells even at high ptiO2 (tissue partial pressure of oxygen). Although the actual yield of oxidative phosphorylation (~ 28 molecules of ATP) is somewhat lower than the theoretical yield (30-32), this functional asymmetry has profound implications. It is deemed that the inefficiency in the energetic yield of glucose fermentation, approximately 14 times lower than that of respiration (2 moles and 28moles of ATP per mole of glucose, respectively), forces cancer cells to an over-expression of GLUT transporters [11], hexoquinase-2 [12] and lactate dehydrogenase -specifically isoenzyme "A" [13]. The extensive reprogramming of energy metabolism undergone by cancer cells explains the intense glucose uptake shown by solid tumors, and is the basis for the Positron Emission Tomography (PET), using the 18 FDG radiotracer, the absorption of which reveals hyper metabolic tissues [14]. In PET-positive tumors, with a Standardized Uptake Value higher or equal to 3 (SUV ≥ 3), glycolysis and glutaminolysis are known to be over expressed by a factor of 10 or higher, even in the presence a ptiO2 high enough to sustain oxidative phosphorylation [15]. Neoplastic cells of pancreatic origin are not the exception [16].

Table 1: Baseline characteristics of patients included in the CISA protocol.

Patient #	Age at Diagnosis	Gender	Metastasis at Diagnosis	Previous Treatment
1	46	M	YES	NO
2	67	M	NO	NO
3	58	F	YES	YES
4	63	F	YES	YES
5	61	F	YES	YES
6	53	F	YES	NO
7	61	M	NO	YES
8	30	M	YES	NO
9	54	M	NO	NO
10	55	F	NO	YES
11	70	F	NO	NO
12	75	M	NO	NO
13	53	M	YES	YES
14	59	M	NO	NO
15	53	M	YES	YES
16	57	F	NO	YES
17	69	M	YES	NO
18	68	M	NO	YES
19	64	F	YES	NO
20	40	M	YES	YES
21	69	F	YES	YES
22	54	M	YES	NO

M: Male; F: Female

This central feature of cancer, the Warburg effect, is the universal phonotypical hallmark of all malignant tumors [17].

In the last decade, these authors have acquired deep functional knowledge on the use of the glucose analog 2-deoxy-D-glucose as an adjuvant in the treatment of highly glycolytic tumors [18]. Also, the intravenous use of pharmacological doses of sodium ascorbate, another six carbon analog, has proved to be selectively cytotoxic for cancer cells of multiple tumor types, both *in vitro* [19,20] and *in vivo* [21,22], including pancreatic adenocarcinoma [23].

The purpose of this study is to determine the impact of the metabolic therapy (CISA protocol) on the one year survival rate of pancreatic cancer patients, thus validating a thermodynamic approach to cancer treatment through competitive inhibition of the HK2, LDHA and GS enzymes with glucose and glutamine structural analogs. To that end, the criterion used is the determination of the one year survival rate after diagnosis (YS) and overall survival (OS) of patients included in the protocol, and the comparison with similar parameters reported in the literature.

Materials and Methods

Since 2009 our Medical Center offers clinical consultation to cancer patients, a fraction of which suffer from exocrine pancreatic neoplasm. These patients were diagnosed by ultrasound, CAT, PET and/or biopsy, as well as tumor markers (CEA, Ca_{19}-9, Neuron-Specific Enolase, LDH and PCR). All suitable patients received detailed information about the therapeutic procedures intended, deciding by themselves (therefore randomly, from our point of view) whether or not to be included in the treatment program. Out of

Table 2: One year survival, overall survival and tumor remisión in patients under the CISA protocol.

Patient #	T1 (months)	Tumor Remission	YS 77,3%	OS (months)
1	3	Partial	YES	26
2	1	Partial	YES	63
3	15	Partial	YES	20
4	0	No	NO	6
5	12	No	YES	16
6	12	Partial	YES	60
7	18	Partial	YES	65
8	3	No	NO	4
9	2	Total	YES	35
10	15	Partial	YES	26
11	1	Total	YES	69
12	3	Partial	YES	21
13	7	No	YES	13
14	9	No	YES	18
15	8	No	YES	24
16	12	No	YES	16
17	2	Partial	YES	24
18	4	Partial	YES	14
19	2	Partial	NO	8
20	12	Partial	YES	25
21	2	No	NO	5
22	3	No	NO	6

T1: Time from diagnosis to beginning of treatment

59 patients with exocrine pancreatic cancer, 22 decided to join the protocol. Informed consent was obtained in every case.

Inclusion/exclusion criteria

Patients included in the study were individuals over 18 years, of both sexes, diagnosed with exocrine pancreatic cancer, with or without metastasis, under no concomitant therapies at the time of joining the CISA protocol. Patients living long enough to receive at least one treatment cycle of 35 intravenous injections were considered for the statistical analysis. The baseline characteristics of the patients, detailed by age, sex, disease stage, metastasis and previous therapies, are described in (Table 1).

Procedure

One Year Survival (YS) after diagnosis and Overall Survival (OS) of patients included in the protocol were assessed. Time periods were expressed in months and defined as: t0, time of oncological diagnosis; t1, time since diagnosis to beginning of treatment with CISA protocol; t2, treatment duration and t3, OS since diagnosis up to study closure. It was determined whether or not patients experienced full or partial remission after completing a treatment cycle. The YS and OS were then assessed and compared to similar time lapses reported in the scientific literature in order to determine treatment impact [24-27].

Results

Twenty two patients were evaluated -9 women and 13 men, mean age 58, 5 years (30-75) - out of which 11 had not undergone any previous treatment (naïve), and 13 presented metastasis at the time of diagnosis. For the group as a whole, YS was 77.3% (17/22), while mean

Table 3: YS and OS of patients with either partial or complete remission, with or without previous treatment.

Patient #	T1 (months)	Tumor remission	YS 77,3%	OS (months)
1	3	Partial	YES	26
2	1	Partial	YES	63
3	15	Partial	YES	20
4	0	No	NO	6
5	12	No	YES	16
6	12	Partial	YES	60
7	18	Partial	YES	65
8	3	No	NO	4
9	2	Total	YES	35
10	15	Partial	YES	26
11	1	Total	YES	69
12	3	Partial	YES	21
13	7	No	YES	13
14	9	No	YES	18
15	8	No	YES	24
16	12	No	YES	16
17	2	Partial	YES	24
18	4	Partial	YES	14
19	2	Partial	NO	8
20	12	Partial	YES	25
21	2	No	NO	5
22	3	No	NO	6

T1: Time from diagnosis to beginning of treatment

Table 4: YS and OS in patients without remission.

Patient #	T1 (months)	YS	OS (months)	Previous treatment
4	0	NO	6	YES
5	12	YES	16	YES
8	3	NO	4	NO
13	7	YES	13	YES
14	9	YES	18	NO
15	8	YES	24	YES
16	12	YES	16	YES
21	2	NO	5	YES
22	3	NO	6	NO

T1: Time from diagnosis to beginning of treatment

OS was 26 months (4-69) (Table 2). Figure 1 shows the distribution of our mortality data. For the 13 patients with complete or partial remission, YS was 92.3% and mean OS was 35.1 months (8-69) (Table 3), whereas in patients with no remission it was 55% and 12 months, respectively (4-24) (Table 4). Regarding the 13 patients bearing metastasis at the beginning of treatment, YS and mean OS were 61.6% and 18.2 months (4-60) (Table 5). According to international reports, mean OS in these patients universally stands at 3 to 6 months (=4.5), which indicates that survival was higher in the metabolic arm of our study by a factor of nearly 4 (18/4.5 months), with an effect size of 0.9. As for the 9 patients with no metastasis at the time of diagnosis, YS stood at 100%, while the mean OS was 36.3 months (14-69) (Table 6). In the case of the 11 naïve patients, the values obtained were 72.7% and 30.4 months (4-69), respectively (Table 7). In the case of the 11

Table 5: YS and OS of patients with metastasis, with or without previous treatment.

Patient #	T1 (months)	YS	OS (months)	Previous treatment	Remission
1	3	YES	26	NO	Partial
3	15	YES	20	YES	Partial
4	0	NO	6	YES	No
5	12	YES	16	YES	No
6	12	YES	60	NO	Partial
8	3	NO	4	NO	No
13	7	YES	13	YES	No
15	8	YES	24	YES	No
17	2	YES	24	NO	Partial
19	2	NO	8	NO	Partial
20	12	YES	25	YES	Partial
21	2	NO	5	YES	No
22	3	NO	6	NO	No

T1: Time from diagnosis to beginning of treatment

Table 6: YS and OS of patients without metastasis, with or without previous treatment.

Patient #	T1 (months)	YS	OS (months)	Previous treatment	Remission
2	1	YES	63	NO	Partial
7	18	YES	65	YES	Partial
9	2	YES	35	NO	Total
10	15	YES	26	YES	Partial
11	1	YES	69	NO	Total
12	3	YES	21	NO	Partial
14	9	YES	18	NO	No
16	12	YES	16	YES	No
18	4	YES	14	YES	Partial

T1: Time from diagnosis to beginning of treatment

Table 7: YS and OS of patients without previous treatment.

Patient #	T1 (months)	YS	OS (months)	Previous treatment
4	0	NO	6	YES
5	12	YES	16	YES
8	3	NO	4	NO
13	7	YES	13	YES
14	9	YES	18	NO
15	8	YES	24	YES
16	12	YES	16	YES
21	2	NO	5	YES
22	3	NO	6	NO

T1: Time from diagnosis to beginning of treatment

patients with any sort of previous orthodox treatment, YS was 81.8, while OS reached an average of 20.9 months (5-65) (Table 8). For patients under 60 years, with or without previous treatment, YS was 83.3% and mean OS was 22.7 months (4-60) (Table 9), whereas 70% of patients older than 60 were alive by the end of the first year, with a mean OS of 29.1 months (5-69) (Table 10). Table 11 summarizes raw data on which statistical analysis was conducted. The resulting YS and OS were compared with the values reported in the main reference data bases which, for the purposes of this study, were considered as the "control group". Resulting data demonstrated an effect size of

Table 8: YS and OS of patients with previous treatment.

Patient #	T1 (months)	YS	OS (months)	Remission
3	15	YES	20	Partial
4	0	NO	6	No
5	12	YES	16	No
7	18	YES	65	Partial
10	15	YES	26	Partial
13	7	YES	13	No
15	8	YES	24	No
16	12	YES	16	No
18	4	YES	14	Partial
20	12	YES	25	Partial
21	2	NO	5	No

T1: Time from diagnosis to beginning of treatment.

Table 9: YS and OS in patients <60 years old, with or without previous treatment.

Pacient #	Age	T1 (months)	YS	OS (months)	Previous treatment	Remission
1	46	3	YES	26	NO	Partial
3	58	15	YES	20	YES	Partial
6	53	12	YES	60	NO	Partial
8	30	3	NO	4	NO	No
9	54	2	YES	35	NO	Total
10	55	15	YES	26	YES	Partial
13	53	7	YES	13	YES	No
14	59	9	YES	18	NO	No
15	53	8	YES	24	YES	No
16	57	12	YES	16	YES	No
20	40	12	YES	25	YES	Partial
22	54	3	NO	6	NO	No

T1: Time from the diagnosis to beginning of treatment

1.13, showed in Figure 2.

Tumor remission was determined through comparative imaging studies -pre and post metabolic treatment- by ultrasound scan, computed tomography and/or PET-TC. The definition of remission was taken to be any measure of decrease of one or more of the diameters of the previously detected tumors. In all the cases where a measurable decrease of one or more tumor masses was observed, there was a correlation with a decrease of the specific tumor markers (CEA, Ca-19, 9, Neuron specific enolase, LDH, PCR).

None of the patients included in this protocol received any concomitant therapy, whether surgical or pharmacological (chemotherapy) throughout the full length of the above-described program or before it. By definition, naïve patients had not undergone any kind of therapy prior to the beginning of the metabolic treatment, whereas the so called non-naïve had previously received some kind of standard therapy, with negative results. Quality of life, regularly assessed following the criteria of the Karnofsky Performance Scale (data not Shawn), proved to be far better than that recorded in the literature as well as the empirical data.

Discussion

Presently, all reported data show pancreatic cancer mortality rate as virtually the same as its incidence [28]. The uniformity of

Table 10: YS and OS in patients >60 years old, with or without previous treatment.

Patients #	Age at diagnosis	T1 (month)	OS (month)	Previous treatment	Remission	Alive
2	67	1	63	NO	Partial	YES
4	63	0	6	YES	No	NO
5	61	12	16	YES	No	YES
7	61	18	65	YES	Partial	YES
11	70	1	69	NO	Total	YES
12	75	3	21	NO	Partial	YES
17	69	2	24	NO	Partial	YES
18	68	4	14	YES	Partial	YES
19	64	2	8	NO	Partial	NO
21	69	2	5	YES	No	NO

T1: Time from the diagnosis to beginning of treatment

Table 11: One-year survival (YS) and mean overall survival (OS) by sub-cohorts.

Groups	YS (%)	Mean OS (interval) (months)
Total number of patients (n=22)	77,3	26 (4-69)
Patients that obtained remission (n=13)	92,3	35,1 (8-69)
Patients with no remission (n=9)	55	12 (4-24)
No metastasis at beginning of treatment (n=9)	100	36,2 (14-69)
Metastasis at beginning of treatment (n=13)	61,6	18,2 (4-60)
Naive (n=11)	72,7	30,4 (4-69)
Previously treated (n=11)	81,8	20,9 (5-69)
Patients under 60 yrs (n=12)	83,8	22,7 (4-60)
Patients over 60 yrs (n=10)	70	29,1 (5-69)

the data reported in the literature allow for a consideration of the statistical universe as "control group". According to a meta-analysis of 30 randomized clinical trials involving 8467 patients, any increase in the Progression Free Survival (PFS) is highly relevant given its strong correlation with OS [29]. As reported by Petrelli et al., the mathematical correlation between the PFS and OS is very high (RS=0.71), with a 0.76 [+/- 2.6] regression slope. This suggests that an agent capable of producing a 10% increase in the PFS could potentially generate a 7.6% [+/- 2.6] in OS increase, which is consistent with our findings. This effect is particularly attractive in this context since a treatment based on metabolic constrictions is essentially innocuous, sparing the host a great amount of systemic damage, thus preserving the organism for subsequent interventions with curative intent.

In terms of statistical analysis, given the invariability of mortality in this pathology, the authors propose that the magnitude of the effect [μOS Treatment – μOS Control]/σ, instead of the statistical significance, should be considered in the assessment of the therapeutic impact of a cancer therapy [30]. It has previously been determined that cancer mortality increases linearly as a function of time. Furthermore, according to the Hardin Jones principle for the analysis of homogeneous cohorts of cancer patients, -regardless of the therapy employed-the primary determinants of mortality of intractable cancers are the intrinsic dynamics of tumor biology [31]. A measure such as the effect size, therefore, should be regarded as a strong indicator of true therapeutic success.

The competitive inhibition of rate-limiting enzymes by means of structural analogs, during induced, acute glucose deprivation, has obvious clinical effectiveness. However, a mechanistic explanation of the effect of this metabolic approach to cancer therapy has not been elucidated yet. It is likely that this phenomenon is partly due to energetic stress in the neoplastic tissue [32]. At the same time, by using intravenous ascorbate, a sudden interstitial and intracellular increase of the Oxygen Free Radicals (H_2O_2, -OH,O-2) has been observed, mediated by the Fenton reaction [33,34]. There is experimental data supporting the notion that this reaction takes place within neoplastic tissue, given the presence of an electron donor (ascorbate) and an abundant transition metal such as iron or copper, in the presence of oxygen -O_2- [35].

Also, D-glucosamine, extensively documented as an antitumor agent [36-39], seems to primarily exercise its effect through injury to the Endoplasmic Reticulum [40,41], while 2-deoxy-D-glucose has shown clear anti metabolic action on neoplastic cells with over expression of glycolysis [42-44].

The above-described structural analogs are essentially innocuous, and have been extensively studied by our group from a pharmacokinetics perspective [15]. In the context of this therapeutic strategy, optimal application requires that patients come to glucose plasma levels under 9 mg/dL, a state we have called nuliglycemia lucidae. At the same time, ketone bodies (betahydroxibutirate) in excess of 2 mM/L must also be present, serving as substitute biological fuel, therefore supporting brain function.

Conclusion

Our Metabolic Therapy of pancreatic cancer has shown an overall one-year survival rate of 72% for the group of patients included in the CISA protocol. Remarkably, patients without metastasis at the time of diagnosis had a one-year survival rate of 100%, a two-year survival rate of 100%, and an impressive three-year survival rate of 55.6%. The magnitude of the effects observed suggests that the treatment program allows for a substantial increase in the one-year survival rate. It should be considered that for the treated group as a whole overall survival reached an average of 26 months, a significantly longer period than that reported worldwide, which stands at 4,5 (3-6) months. Even though this analysis focuses only on the quantitative impact of the treatment on survival, it is important to mention that a better quality of life in these patients was observed during metabolic therapy. A significant finding from a clinical perspective is that the results obtained are reached without immuno suppression, febrile neutropenia or liver/kidney toxicity, frequently associated to cytotoxic chemotherapy, as well as other side effects of the conventional approach.

Two significant limitations in this study were the small size of the sample (N) and the heterogeneity of the clinical stages among the patients at the beginning of the treatment, therefore subsequent recruitment and appropriate distribution in homogeneous cohorts are necessary for a more relevant report. At the same time it is hoped that a better metabolic characterization of each host scheduled to receive the CISA protocol be reached, as well as a deeper understanding of the specific metabolic phenotype of each tumor. These distinctions would enhance the therapeutic effect of the CISA system, and thus, the overall survival of pancreatic cancer patients.

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