Insulin Potentiation Therapy in the treatment of malignant neoplastic diseases: a three-year study

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ABSTRACT

Even after decades of scientific research, application of chemotherapy still puts modern medicine in a difficult position. Many problems accompany administration of chemotherapeutic drugs, some of the most important of which are the numerous toxic side effects and the development of chemoresistance. Unfortunately there is still no adequate solution and exploration continues. Despite the widespread tendency to include a variety of new chemotherapeutics in different combinations, shown also in a great number of clinical trials, the progress related to the toxicity and effectiveness of the treatment is slow-going and unsatisfactory (1).

In the search for a new approach to lower the toxicity and to improve the effectiveness of the treatment, in the year of 2006 we introduced the method of Insulin Potentiation Therapy (IPT) in our practice. The theory basis and the gathered experimental data on insulin's mode of action, as well as its application in practice, show that IPT is a promising method with low toxicity. Moreover, it allows a selective and physiological approach (2), (3), (4), (5), (6), (7). These important features attract the attention of more and more physicians from all around the world.

In this report we present the results of our three-year experience applying Insulin Potentiation Targeted Therapy Low Dose (IPTLD) in the treatment of 196 patients with different neoplastic diseases, 148 of which in an advanced metastatic state.

Our results showed that patients tolerated IPTLD very well and without serious side effects. The latter were usually minimal and did not require treatment interruption or additional medication. The laboratory tests did not show any significant toxicity. Eighty eight (81%) out of 108 followed-up patients with advanced metastatic illness declared a subjectively significant improvement in their quality of life. Future extended experimental data and

clinical trials would contribute for a complete understanding of the therapeutic potential of IPTLD, as long as its role in the complex therapy of neoplastic disease.

INTRODUCTION

The basic principle of conventional chemotherapy is the administration of maximum tolerated doses in extended intervals of time. Even though many new chemotherapeutic drugs and combinations are being developed and used in numerous clinical trials, advancement is slow-going and arduous. The problems, associated with high toxicity, chemo resistance and the lack of significant prolongation of life expectancy are still unresolved (8), (9), (10), (11).

During the last decade of searching for a new strategy to lower treatment toxicity, a new direction came out. The so called "metronome chemotherapy" is applied in smaller doses and at shorter intervals. The initial experimental and clinical results on its action are promising and prompt further investigation into that new area (6), (8), (9).

Another method involving low doses of conventional chemotherapeutics administered in short intervals represents a combination between standard chemotherapy protocols and insulin, given intravenously. In the last few years this method became popular as Insulin Potentiation Therapy Targeted Low Dose (IPTLD). This method offers a physiological approach to the human organism and in the same time a selective method of targeting malignant cells, which leads to an insignificant treatment toxicity (2), (3), (4), (5).

The method of IPTLD was empirically created in 1932 by the Mexican military doctor Donato Perez Garcia, who has successfully applied it into clinical practice for more than three decades. The theoretical basis of IPTLD mechanism of action is developed and presented in two consecutive publications by D. Perez Garcia et al. (2), (3). In the last few decades the method gained increasing popularity and is being practiced by more and more physicians all over the world.

We would like to present in this report our three-year clinical experience with IPTLD in the treatment of a variety of neoplastic diseases.

MATERIALS AND METHODS

From March 2006 until August 2009 we administered IPTLD to 196 cancer patients. All subjects had biopsy-proven diagnoses. Eight patients (4%) were treated for locally advanced tumors combined with surgery and 188 patients were treated for advanced metastatic disease.

Detailed information and a medical consultation were given to every patient. Each subject was enrolled in the treatment after signing an informed consent. Table 1 shows the clinical characteristics of the subjects involved. Table 2 shows the location of the neoplastic disease.

Before initiation of therapy, detailed information was gathered for each subject involved in this study, including: imaging tests (done in different medical institutions – CT scans, MRI, ultrasound, bone scintigraphy, chest X-Rays), laboratory tests (complete blood count, serum albumin, blood sugar, urea, creatinin, cholesterol, blood mineral balance, liver tests, coagulation status, CRP, urine samples, tumor markers including ferritin). Control lab tests, including tumor markers were run after the 6^{th} IPTLD and after every following 4^{th} IPTLD. Control imaging test were run after the 10^{th} procedure and on the 3^{rd} and 6^{th} month after therapy. When needed, control lab tests were run after the 3^{rd} procedure.The patients' status before the treatment was evaluated using the Karnofski Performance Status scale. Before initiation and every month during the therapy the patients filled in, in written form, the Beretta Self Compilation Questionnaire, needed for the monthly evaluation of their subjective status (12).

Short acting Insulin 0.4 units/kg body weight was used in combination with various types of cytostatic drugs. The medications were those, used in conventional chemotherapy schemes, only their dosage was decreased tenfold. In some cases, when the patients had undergone previous standard chemotherapy, which lead to chemoresistence, we applied new chemotherapeutic combinations. In cases of tumors with aggressive behavior we used alternating chemotherapy. Our course of treatment consisted of 6 IPTLD procedures, one per week for 6 consecutive weeks. Afterwards we conducted lab tests. In case of improvement, we applied another 4 IPTLD procedures, one in every 10 days. After that we administered IPTLD between progressively increased intervals - once every 2, 3 or more weeks.

Medication during the intervals included hepatoprotectors, antiangiogenesis drugs, Dexamethasone, COX-2 inhibitors, low doses of Cyclophosphamide. In case of severe intoxication, in the intervals between IPTLD we applied infusion therapy and ozone therapy (13).

Detoxification was an essential element of the treatment and included the following components: diet, caffeine enema, antioxidants, ozone therapy, laser and UV blood radiation.

We encountered a myriad of practical challenges for the 3-year period of practice with IPTLD. Some of them included incomplete imaging and lab tests data and some patients who refused further treatment. For those reasons we found ourselves unable to use all available criteria while evaluating treatment efficacy. Eventually, we based our assessment on the number of subjectively improved patients, laboratory tests and tumor markers, the quality of life of the patients and the side effects of the treatment.

RESULTS

Forty Eight of 196 patients (24.4%) refused further treatment before the 6th application. That was due mainly to financial problems or emotional distress. Twenty One of 196 patients (10.7%) refused further treatment before the 10th procedure. The average number of IPTLD applications, when the patients continued their treatment after the 6th therapy was 13.

Our patients tolerated IPTLD quite well. The side effects observed were general fatigue and lethargy on the day of treatment. Four of the 148 patients who had more than 6 IPTLD procedures (1.3%) had nausea and vomiting in light to moderate degree. The next day those side effects disappeared. Two of 148 patients (1.36%) had allergic reaction to vitamin B complex which was easily controlled by application of corticosteroids.

Patients with normal blood count tests did not have any significant changes. Hemoglobin (Hb) levels slightly decreased in 65 (43.9%) of 148 patients. Only two of 148 patients with initially low Hb level needed blood transfusion during the treatment. Liver enzymes showed slight and temporary elevation in 23 (26%) out of 86 patients with normal liver tests before the treatment, which did not affect the patients' subjective status. These changes in Hb and liver tests coincide with grade 0 according to ECOG Toxicity Criteria (14).

Four of 148 patients with chronic renal failure had higher levels of serum creatinin, which did not disrupt the treatment progress itself. No one of the treated patients discontinued therapy or needed any intervention due to side effects.

None of the eight patients treated for locally advanced tumors combined with surgery developed a recurrent tumor for a mean follow up period of 11 months. In that group there was just one case of a recurrent tumor - a patient with breast cancer who had undergone an operation for a 6 cm lesion. She was brought to our medical center and given 15 IPTLD applications. Imaging tests did not show tumor presence. Subsequent surgery revealed a residual tumor of 1.5 cm. After the IPTLD the patient went into a remission for 19 months.

However, the small number of patients and the short follow-up period does not allow drawing substantiated conclusions concerning the effectiveness of IPTLD as treatment in such cases.

Therapy effectiveness, according to Beretta symptomatic index was investigated in 108 patients. Twenty (18.5%) of them had no significant symptomatic index change. Forty Nine (45.3%) out of 108 patients presented symptomatic index score before the treatment over 26 points (from 26 up to 50, with a maximum of 52). After the 6th application of IPTLD the symptomatic index values lowered by an average of 12 points. Four (3.7%) of 108 patients had completely normal index. Figure 1 shows Beretta symptomatic index results.

Lowering of tumor markers was observed in 45 (53%) out of 85 patients followed up after the 6^{th} application. Seven (8%) of 85 had completely normal tumor markers values.

Nine patients presented with type II diabetes. During the treatment eight of them (89%) had their blood sugar levels normalized.

DISCUSSION

Sixty percent of the patients with metastatic tumors felt subjective improvement immediately after the first application. Eighty eight out of 108 treated patients (81.5%) had significant general improvement and decreased subjective complaints after the 6^{th} application. The results showed a significant improvement in the quality of life. The longest remission period we registered was in a 60 years old female patient who had undergone an operation for gastric cancer. She was diagnosed with a metastatic disease after being discovered to have secondary lesions in her liver. After just one conventional chemotherapeuthical procedure, the patient had experienced serious toxic side effects. She was enrolled in our program and underwent 10 IPTLD. Imaging and lab test did not show presence of metastases or increased tumor markers. At present the patient is still in a remission, fit for work and with an excellent quality of life. Three of 108 patients with advanced metastatic disease had a remission of more than 24 months.

Treatment results depended on the disease stage and on whether preexisting chemo- and radio therapy had been administered. We have presented our results from treating such patients in a separate publication (6). The fact that those patients had successful improvement after failed previous chemo- and radio therapy is not only a proof for the efficacy of IPTLD, but a perspective for its wider application in the practice of oncology. A 56-year-old patient treated

for advanced metastatic hormone - resistant prostate cancer had a complete remission for a follow up period of 20 months (6).

Insulin Potentiation Therapy can be applied to diabetic patients. We have the impression that in those cases therapy effectiveness is somewhat lower. However the treatment is easily tolerated, without any significant side effects. In two cases with type II diabetes we applied their usual morning insulin dosage before IPTLD. During the treatment 8 out of 9 diabetic patients had permanently lower blood sugar levels.

Patients easily tolerated IPTLD. Serious side effects were not registered, except for two patients with preexisting anemic syndrome, which required blood transfusion. The usual side effects (fatigue and lethargy on the day IPTLD was administered) were minimal and didn't require treatment interruption or additional medications. On the next day all complaints disappeared. The lab control tests did not show any significant toxicity.

Treatment with IPTLD can easily be conducted on patients even with altered physical status, preexisting serious conditions or who had been ruled out from conventional chemotherapy schemes.

We are still searching to improve IPTLD efficacy and outcome, as well as the optimal supporting treatment after IPTLD remission. The experience we have obtained so far in treating metastatic tumors gives us reason to believe that the efficacy of IPTLD could be even higher than expected. We see beneficial opportunities in three main directions: 1) adding new and effective methods for detoxification to IPTLD, 2) including reachable and effective antiangiogenesic and immunomodulating drugs in IPTLD schemes, and 3) combining IPTLD with other methods like thermotherapy, electrotherapy, photodynamic therapy, immunotherapy and others.

Based on the available theoretical data, the gathered practical knowledge by the physicians who apply the method, as well as on our own humble experience, we sincerely believe that the method presents a compelling opportunity for solving the problem with chemotherapy's toxicity, for improving treatment effectiveness and quality of life.

The results we achieved, applying IPTLD, and most importantly its lower toxicity enabled us to apply it as a leading method in the therapy of cancer patients in our practice.

Future extended experimental data and clinical trials would contribute for a complete understanding of the therapeutic potential of IPTLD, as long as its role in the complex therapy of neoplastic disease.

ACKNOWLEDGEMENTS

The authors would like to express their gratitude to Latchezar Avramov, PhD who contributed to this work.

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Total number of patients	196
Age (mean)	57
Sex, m/fm ratio	1.32
Karnovsky Performance Scale (mean)	70
Preceding Surgical treatment	108
Preceding Hormonal Therapy	11
Preceding Chemotherapy	36
Preceding Radiotherapy	16
Stage I	24
Stage II	39
Stage III	62
Stage IV	63
With local metastases	107
With distant metastases	105

Table 1. Clinical characteristics of involved subjects.

Lungs	30
Mammary gland	26
Prostate gland	20
Stomach	19
Urinary bladder	14
Large intestine	10
Ovaria	14
Pancreas	9
Uterus	13
Liver	4
Malignant melanoma	4
Head and Neck	7
Others	53

Table 2. Location of the tumor

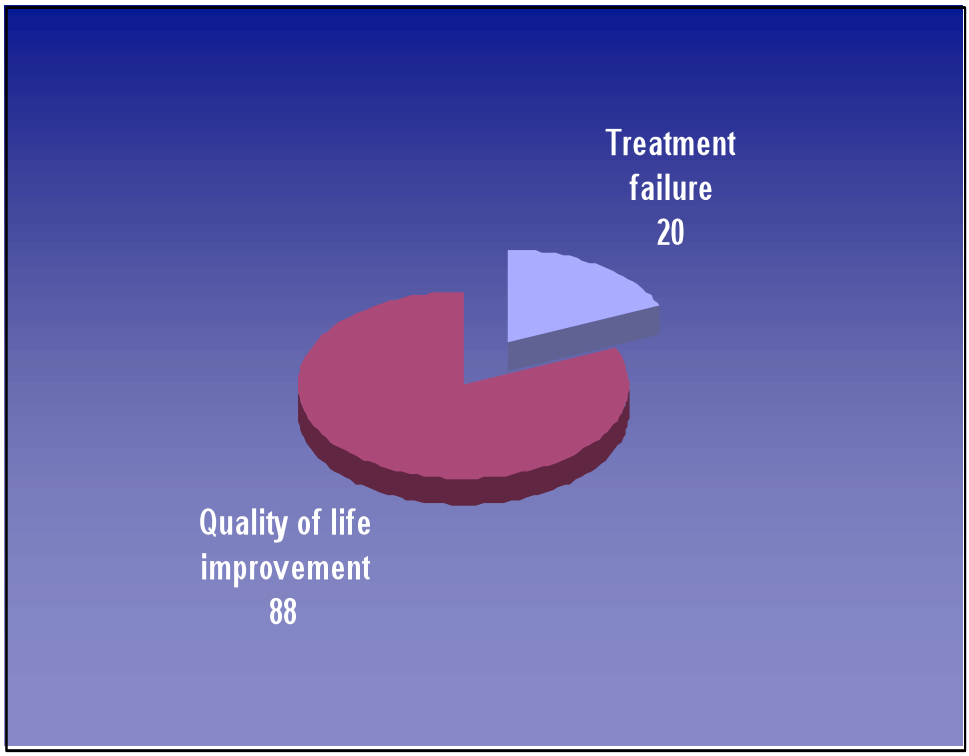

Fig.1 Therapy effectiveness, according to Beretta symptomatic index, followed up in 108 patients