Low dose chemotherapy in combination with insulin for the treatment of advanced metastatic tumors. Preliminary experience

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Summary

Toxic effects and chemoresistance are serious problems concerning chemotherapy administration. Until now adequate solutions have not been found. In the past few years, while searching for possibilities to decrease toxicity, chemotherapy given in low, frequent doses - a novel strategy called “metronomic” administration - showed promising results.

There is also another method for applying low doses of chemotherapeutics at short intervals, called Insulin Potential Therapy (IPT). It combines standard chemotherapy schemes, using lower doses of anticancer drugs and the hormone insulin which is administered intravenously (i.v.).

We present hereby 3 cases of our original practice, which demonstrate the efficiency of IPT in the treatment of metastatic tumors, following failure of standard chemotherapy.

Key words: insulin enhanced antitumor response, insulin potential therapy

Introduction

Guided by the idea for achieving maximum treatment efficiency of malignant diseases, standard chemotherapy uses maximum tolerated doses at 21-28 day intervals. While high doses cause increased toxicity, the long intervals between cycles lead to chemoresistance of tumors. Both factors are serious problems and a basic premise for reducing the therapeutic index of the treatment given [1-3].

Searching for possibilities to reduce the toxic effects of chemotherapy without lowering its antitumor efficacy, intensive research have been carried out in the last couple of years about the application of chemotherapy in low doses at short intervals - the so-called metronomic chemotherapy. Experimental and some clinical observations show substantial possibilities for reducing treatment toxicity while maintaining its efficiency at the same time [3-5].

The application of low-dose chemotherapy of increased frequency is also possible by using another method, the IPT, which combines the administration of standard chemotherapy regimens with i.v. administered insulin, by using 10 times lower doses of chemotherapeutic drugs and closer intervals between courses [6,7].

Since 2003 we have been actively investigating the possibilities for reducing the toxicity of standard chemotherapy, and since April 2006 we began to use IPT in our practice for the treatment of ambulatory cancer patients. For the period April 2006 - September 2008 in the Medical Center of Integrative Medicine more than 105 patients have been treated with IPT and the results will be communicated in future publications.

We present herein 3 cases of our original practice, demonstrating the potentialities of IPT in the treatment of metastatic tumors where standard chemotherapy had failed.

Case presentations

Case 1

A 44-year-old female was operated on in July 2004 for breast cancer with left quadrantectomy and axillary...
zymes during IPT. Tumor markers on 18.02.2008 were:
CEA 41.7 and CA15-3 41.8; CA15-3 of 24/04/2008
was 46.5.
Repeat abdominal CT and bone scans showed
about 20% reduction of the bone and liver metastatic
lesions.
In March 2008 she complained of pain in the right
coxofemoral articulation. We then readministered 3
weekly IPT courses with docetaxel (3.6 mg/m²)
and carboplatin (25 mg/m²) till 02.04.2008. The pain
completely disappeared.
We followed the patient until June 2008; after that
date she was lost to follow up.

Case 2
A 34-year-old female presented on April 14, 2008
with right breast cancer, T2N1M1 (multiple bone me-
tastases and axillary nodal involvement). No further
details were available.
She complained of bone pain. Tumor marker CA
15-3 was elevated (116 IU/ml, normal up to 32). The pa-
tient was put on chemotherapy with epirubicin,
5-fluorouracil and cyclophosphamide. Only one course of
treatment was administered because the patient refused
further chemotherapy due to severe side effects. Pallia-
tive treatment was given with zoledronic acid, ketopro-
fen, and dexamethasone without success. The pain in
the thoracic and lumbar vertebrae progressed, making
movements difficult.
Status before IPT treatment: KPS 70, symptomatic
index 20 points. Repeat CA15-3 was 125.13.
In April 2008 the patient was put on IPT with in su-
lulin (0.3 U/kg), cyclophosphamide (0.10 g/m²), me tho-
trexate (9 mg/m²) and 5 fluorouracil (28 mg/m²) with
40% hypertonic glucose i.v. at 5-day intervals. On non-
treatment days the patient was given antiangiogenic
therapy as previously described. No side effects except
the usual weakness and sleepiness on the day of the pro-
cedure were noticed and lab examinations showed no
significant toxicity.
After the 3rd IPT course a subjective improve-
ment was observed in the patient’s condition - decrease
in the restlessness, weakness and the pain in the right
coxofemoral articulation. She gained 2 kg. After the 7th
IPT course the pain disappeared and the motor activity
was almost entirely restored. The patient regained her
working capacity. Symptomatic index from May 2008
decreased to 2 points.
During IPT treatment no serious side effects were
noticed. The only complaints were weakness and sleepi-
ness for no more than a day.
Lab examinations did not show significant toxicity
with the exception of insignificant increase in liver en-
After the 3rd course there was significant improvement in his general condition (KPS 90), less complaints and good motor activity. After the 5th IPT course all complaints had subsided. The symptomatic index in March 2008 was 6 points.

Bone scan in April 2008 showed that the number of hot spots had decreased by more than 50%. CT scan on June 2008 showed complete remission of lung metastases and reduction in the number and size of osteoblastic lesions in vertebrae and pelvic bones. Nodal disease in the upper abdomen entered complete remission. In May 2008 PSA fell to 5.12 ng/ml and alkaline phosphatase to 278 U/L. The symptomatic index in September 2008 was 6 points.

Lab findings did not show significant toxicity. The only complaints during treatment were weakness and sleepiness on the day of therapy. The next day these symptoms disappeared.

At the moment the disease is stabilized and the patient is working actively and receiving maintenance therapy regularly.

Discussion

IPT was empirically developed in 1930 by Donato Perez Garsia who successfully applied it for 41 years for the treatment of chronic and oncological diseases. Later his practice was continued by his son and grandson, and now the method gains more and more popularity and is being practised by a growing number of physicians and clinics all over the world.

The theoretical conception of the IPT mechanisms was presented in two publications by Ayre Perez Garcia y Bellon and Perez Garcia, in 1986 and 2000 [6,7].

The same authors published in 1990 a case, demonstrating complete tumor regression of ductal carcinoma of the breast in a 32-year-old woman with a discussion of the medical theory behind IPT [15].

In 2003 Lasalva-Prisco and associates published the first clinical study for the application of insulin in combination with methotrexate in patients with breast cancer [16].

The leading role for the effectiveness of the method is played by insulin for non-diabetic purposes. Despite that not all actions of insulin have been fully understood, after the 1960s a considerable knowledge has accumulated indicating that this hormone together with its well-known effect of lowering the level of blood sugar, also exerted a serious impact on the entire human metabolism. Research established that insulin has 5 basic effects:

- Increases cell membrane permeability;

- Influences the metabolic processes with a number of
physicochemical changes which help the recuperating processes;
- Causes profound changes as it stresses the basic cell metabolism and facilitates the healing process;
- Facilitates the transport of intra- and extra-cellular fluid and improves the elimination of toxic products;
- There are also other endocrine effects: direct stimulation of the adrenal medulla, resulting in an increased secretion of epinephrine and glucocorticoid hormones; also increased ACTH secretion by the pituitary [6,7,17].

A number of articles [7,15-19] shows that insulin also influences the tumor cells. As a result of the current level of knowledge for the effects of insulin in tumor biology, the following conclusions could be drawn:
- The increased cancer cell membrane permeability allows increase of intracellular levels of antitumor chemotherapeutics.
- Insulin exerts effects on the intracellular metabolism of the tumor cell by increasing the number of tumor cells in the S-phase in which they are more sensitive to chemotherapeutics.
- The increased number of insulin receptors of the tumor cell - in contrast to the normal one - makes it possible the selective impact of the previous two factors to predominate in the tumor cell [7,17,19-22].

Despite the serious achievements in revealing the intimate mechanisms of insulin in the human body, we still have not reached the full depth of knowledge. Future experimental studies will probably give new perspectives for an effective application of insulin in clinical practice.

In searching for new ways to decrease the toxicity of chemotherapy, in the beginning of 2006 our team began to apply this method, and over 90% of our patients were with metastatic tumors, most of them after unsuccessful standard chemotherapy and radiotherapy.

To illustrate our preliminary experience we presented 3 cases of different tumors; what was common in all of them was that they had very advanced metastatic disease and failure of the previous standard conventional treatment. In those cases we achieved remission for 15, 21 and 8 months, respectively. The first patient was lost to follow up after June 2008 and the other two are in remission until now, receiving maintenance treatment. Their quality of life improved rapidly after the first 2-3 courses and gave the patients the opportunity to restore their normal work activity after 2-3 months from the beginning of treatment. The third patient was additionally treated with LHRH agonist [17,23].

Treatment was very well tolerated, the only complaints being weakness and sleepiness during the first day. Lab examinations showed no significant toxicity. In our 3 patients we observed insignificant increase of liver function tests in the first 6 weeks, while these normalized without any additional measures during treatment.

To our opinion the presented cases are indicative of the therapeutic potential of this method with no serious toxicity. We consider that it is possible to apply IPT after unsuccessful standard chemotherapy and radiotherapy.

More future experimental and clinical studies would help elucidate the therapeutic potential of IPT and the place and role of this method in the combined treatment of oncological diseases.

References