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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

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lymph node dissection. Histology showed invasive ductal carcinoma and axillary nodal metastases (T2N1M0). Postoperatively adjuvant chemotherapy (epirubicin, cyclophosphamide, and 5- fluorouracil, 4 courses) in combination with radiotherapy and hormone therapy were administered. In May 2006 multiple painful bone metastases appeared and, despite readministration of the previous regimen, the disease progressed and the patient was referred for symptomatic treatment.

Lab examinations before IPT treatment showed (February 2007) multiple osteolytic metastases throughout the skeleton (bone and CT scan) and liver metastases (CT scan). Lungs were normal (CT scan).

Other lab examinations were as follows:

Full blood count and diff. normal; ESR 34; alkaline phosphatase 316 U/L (range 100-290); γGT 47 U/L (normal up to 39); CA 15-3 183.5 IU/ml (normal up to 25); CEA 129.9 ng/ml (normal up to 3.4); ALT-AST normal, bilirubin 12.5 μmol/L (normal up to 6.8).

The patient's Karnofsky performance status (KPS) was 60. She complained of pain in her back, pelvis and right shoulder, difficult breathing, physical weakness, cramps and limited movements in the right lower limb. Her temperature was about 38.2° C and she felt restless and depressed. Symptomatic index before treatment was 32 [8].

At the beginning of March 2007 the patient underwent ambulatory IPT treatment with insulin (0.3 U/kg) and, at the onset of hypoglycemia, cisplatin (6 mg/m^2), and gemcitabine (100 mg/m^2) with 40% hypertonic glucose i.v. at 5-day intervals. For interim treatment of IPT we included antiangiogenic therapy [9-14] (dexamethasone 20 mg, cyclophosphamide 50 mg p.o., doxycycline 100 mg, silymarin 3×140 mg, meloxicam 2×7.5 mg). Seven courses of IPT with cisplatin and gemcitabine, and after that, 18 courses of IPT with docetaxel 3.6 mg/m^2+vinorelbine 3 mg/m^2 were administered. The first 4 courses of the second scheme were at 7-day intervals, and then, in maintenance therapy, at 2- 3- and more week intervals.

After the 3rd IPT course a subjective improvement 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 sleepiness for no more than a day.

Lab examinations did not show significant toxicity with the exception of insignificant increase in liver enzymes 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/m^2) and carboplatin (25 mg/m^2) 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 metastases 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 patient 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. Palliative treatment was given with zoledronic acid, ketoprofen, 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 insulin (0.3 U/kg), cyclophosphamide (0.10 g/m^2), methotrexate (9 mg/m^2) and 5 fluorouracil (28 mg/m^2) 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 procedure were noticed and lab examinations showed no significant toxicity.

After the 3rd IPT course a subjective improvement in the patient's condition was noticed with complete disappearance of pain. After the 6th course we continued with maintenance therapy every 2-3 weeks. Up until now 17 IPT courses have been administered.

Control radioimaging studies indicated significant decrease in the number and size of bone lesions (more than 50%), and normal mammography/ultrasound of the right breast, while clinical complete response was noted in the axillary lymph nodes.

Symptomatic index in September 2008 was 10 points. Consecutive CA 15-3 estimations: 40.36 in

07.05.08; 31.62 in 23.05.08; and 14.23 in 06.08.08.

For the moment the patient is stabilized and regained her working capacity. A repeat biopsy of the right breast was recommended, which has not been done until now. She is on maintenance therapy.

Case 3

A 52-year-old male was admitted to the hospital because of abdominal pain and icterus, and was operated on in January 2008 (cholecystectomy). During the operation enlarged lymph nodes were found in the region of hepatoduodenal ligament and the head of the pancreas. Histology from the lymph nodes showed high to moderate grade carcinoma of the prostate. CT scan before the operation showed multiple bone and pulmonary metastases.

During the postoperative period the patient started complaining of difficulty in breathing, physical weakness, whilst pain was deteriorating.

Postoperatively, hormonal treatment with cyproterone acetate was administered, followed by bilateral orchiectomy. Despite treatment, lower backache and pain in the pelvis and right shoulder, difficult breathing and physical weakness persisted and became more intense.

Results before IPT treatment: Chest x-ray (January 2008): metastatic bilateral hilar lesions 20-30 mm in size; bone scan (January 2008): metastatic lesions in vertebrae (scan didn't include pelvic bones); abdominal CT scan (February 2008): multiple abdominal and pelvic conglomerated lymph nodes with max size of 30 mm; diffuse osteoblastic bone metastases.

Other lab results (February 2008): platelets 438,000 (normal 140-400,000); ESR 76 mm (normal up to 15); alkaline phosphatase 1177 U/L (normal 100-290); AST 328 U/L (normal up to 40); ALT 82 U/L (normal up to 40); γGT 77 U/L (normal up to 60); total bilirubin 19 μmol (normal up to 17); PSA 44.78 ng/ml (normal up to 4).

Status before IPT treatment: KPS 60. Lower backache and pain in the pelvis and right shoulder, difficult breathing, physically weak, cramps and extremely limited movements of the right lower limb. Continuous fever around 38.2° C. The patient felt restless and depressed. The symptomatic index before treatment was 32 points.

In February 2, 2008 the patient started outpatient treatment with insulin (0.3 U/kg) and docetaxel (3.6 mg/m^2) with 40% hypertonic glucose i.v. at 5-day intervals. On non-treatment days, he was given antiangiogenetic therapy as previously described, antioxidants, and LHRH agonist (Zoladex) was administered monthly. Up until now 12 IPT courses have been administered. 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.

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