

LongLife Newsletter

Insulin-induced enhancement of antitumoral response to methotrexate in breast cancer patients

It has been reported that insulin increases the cytotoxic effect in vitro of methotrexate by as much as 10,000-fold. The purpose of this study was to explore the clinical value of insulin as a potentiator of methotrexate. Patients and methods: Included in this prospective, randomized clinical trial were 30 women with metastatic breast cancer resistant to fluorouracil + Adriamycin + cyclophosphamide and also resistant to hormone therapy with measurable lesions. Three groups each of ten patients received two 21-day courses of the following treatments: insulin + methotrexate, methotrexate, and insulin, respectively. In each patient, the size of the target tumor was measured before and after treatment according to the Response Evaluation Criteria In Solid Tumors. The changes in the size of the target tumor in the three groups were compared statistically.

Results: Under the trial conditions, the methotrexate treated group and the insulin-treated group responded most frequently with progressive disease. The group treated with insulin + methotrexate responded most frequently with stable disease. The median increase in tumor size was significantly lower with insulin + methotrexate than with each drug used separately.

Discussion: Our results confirmed in vivo the results of previous in vitro studies showing clinical evidence that insulin potentiates methotrexate under conditions where insulin alone does not promote an increase in tumor growth. Therefore, the chemotherapy antitumoral activity must have been enhanced by the biochemical events elicited in tumor cells by insulin.

Conclusions: In multidrug-resistant metastatic breast cancer, methotrexate + insulin produced a significant antitumoral response that

was not seen with either methotrexate or insulin used separately.

Introduction

It is known that slowly growing cancers have tumor cell populations with a low growth fraction and are less sensitive to chemotherapy than rapidly growing tumors with high-growth fractions [1]. Slowly growing malignancies have relatively more cells in a noncycling status and fewer cells in a cycling status than rapidly growing malignancies. It has been demonstrated that insulin as a pharmacological agent induces the switch from a noncycling to a cycling status in tumor cells [5]. In MCF-7 human breast cancer cells, insulin has been shown to increase the cytotoxic effect of methotrexate up to 10,000-fold in vitro [1]. Ellipticine uptake is also increased by insulin [9]. It has been suggested that insulin is effective in potentiating most chemotherapy drugs.

Patients and methods

The study was conducted in 30 patients with breast cancer admitted to medical centers that reported medical data to the Cooperative Trials Center (CTC) of PharmaBlood, R&D Department, Florida. A prospective, randomized trial was carried out. All patients met the following eligibility criteria: histologically confirmed breast carcinoma, metastatic stage (M1); age 74 years; and adequate hematological function (WBC count $\geq 4000/\text{ll}$, neutrophil count $\geq 2000/\text{ll}$, hemoglobin level ≥ 9.0 g/dl, platelet count $\geq 10 \cdot 10^4/\text{ll}$), renal function (serum creatinine ≤ 1.5 mg/dl, 24-h creatinine clearance ≥ 60 ml/min), liver function (total bilirubin ≤ 2.0 mg/dl, serum transaminases not more than twice the upper limit of the normal range), and respiratory function ($\text{PaO}_2 \geq 60$ Torr). The patients included had measurable lesions, as required by the Response Evaluation Criteria In Solid Tumors (RECIST) system of tumor assessment [13], and if they had a positive estrogen

receptor status, they had been treated with and become resistant to hormone therapy. All patients included in the study had progressive disease (RECIST criteria) after chemotherapy with at least four series of fluorouracil + Adriamycin + cyclophosphamide (FAC) and had not been treated with any other chemotherapy. They were randomly allocated to three groups of ten patients each: group 1 was treated with insulin + methotrexate as described below, group 2 was treated with methotrexate without insulin, and group 3 was treated with insulin without methotrexate. Written informed consent, including detailed information about risks and benefits, was approved and signed by all the patients included in the study. Central computerized remote randomization was performed, with patients being allocated to one of the groups through random sequence generation by the permuted block method. An assessment of the results after 30 patients had completed the trial showed that this sample size was enough. The patients were recruited from two oncological medical centers in Montevideo, Uruguay (first at the National Cancer Institute and then at Interdoctors Medical Center), both of which participated with their data in the network operated and sponsored by the Cooperative Trials Center (CTC) of PharmaBlood R&D Department. The institutional ethics committee of PharmaBlood and the institutional review boards of the participating medical centers approved the trial. The ethical reviewers considered that an 8-week delay before starting second-line chemotherapy after FAC had failed in all the patients

I n s i d e S t o r y H e a d l i n e

included in the trial was acceptable. This determination was consistent with the standard of care in this clinical situation which has been recently well summarized [3]: Despite almost 30 years of clinical cancer research, the true impact of second and subsequent lines of chemotherapy on the outcome of metastatic breast cancer patients, especially on the duration of survival, is still unknown. In the virtually incurable metastatic setting, issues link quality of life and patients preferences gain particular relevance. The accepted protocol was resubmitted to the committee for review in order to obtain approval for treatment of patients with insulin alone considering the potentially harmful effect through the activation of receptors for insulin/insulin-like growth factors. The committee confirmed the approval on the basis of reports of no harmful effect of this treatment [6, 7]. The results of the study confirmed the committees criteria because no significant differences were found in tumor growth either between the insulin-alone group and the methotrexate-alone group or between before and after treatment in the insulin-alone group. Treatment of all the patients included in the study received two 21-day courses of treatment separated by a 7-day interval without treatment between courses. In group 1, the treatment course was intravenous human recombinant insulin (0.3 U/kg body weight every other day) followed 20 min later by a 15-min intravenous infusion of methotrexate (2.5 mg/m² in 50 ml 30% glucose). If symptomatic hypoglycemia was observed, the 30% glucose solution containing methotrexate was infused immediately. An oral glucose supplement was also prescribed to prevent delayed hypoglycemic symptoms. In group 2, insulin was omitted and methotrexate was administered intravenously at the same dose and in the same solution (2.5 mg/m² in 50 ml 30% glucose) as in group 1. In group 3, methotrexate was omitted, insulin was administered at the same dose as in group 1, and 30% glucose solution was also administered intravenously 20 min after insulin or sooner if hypoglycemic symptoms were evident. Tumor growth assessment After 8 weeks (two 3-week courses plus 1 week

interval after each course), the response to treatment was assessed in each patient using RECIST criteria [13]. The sum of the longest diameter of measurable target lesions and the number of non-target lesions were recorded immediately before and after this 8-week period. skin nodules and palpable lymph nodes were measured using calipers. Lung and liver target lesions were measured by a CAT scan. Responses were confirmed by repeating the assessment 4 weeks after status assignment. Three independent reviewers performed all image measures (Telemedical Organization, North Miami Beach, Fl.) The distribution of RECIST status (progressive disease, stable disease, or remission) in each group was recorded. This distribution was dependent on treatments that showed statistical significance according to the Chi-squared test. The data from the RECIST measurements of the change in tumor size of the patients in each treatment group, expressed as a percentage of pretreatment measurements, were compared using Students test. Additionally, increases in tumor size were expressed as a proportion of the initial value and analyzed by the two-proportion test comparing pairs of groups: group 3 vs group 1, and group 2 vs group 1. The sample size was assessed after analysis of the results when the trial was finished for the 30 patients allocated to the three groups. The above pairs of groups were analyzed for the proportion of progressive disease in each. Ten patients in each group was the required sample size for an 80% chance of rejecting the hypothesis of equal proportions at the 0.05 level of significance when the true proportions were those shown by the study. Statistical analysis was performed using Stats Direct software and an independent expert was consulted.

Results

The characteristics of the patients included are shown in Table 1. The three groups were comparable in the most relevant prognostic parameters for the clinical condition studied. Previous treatments were also comparable. The similar range of sizes of target lesions measured before treatment was especially significant, allowing the change in size to be measured as a percentage of initial size. Figure 1 shows the RECIST status assessed under the study conditions. Progressive disease was the most frequent response in two of the three groups: in group 2 (treated

with methotrexate alone) there were seven progressive disease and three stable disease, and in group 3 (treated with insulin alone) there were eight progressive disease and two stable disease. In group 1 (treated with insulin+methotrexate), stable disease was the most frequent response (nine stable disease, one progressive disease). The distribution of RECIST type responses (stable disease and progressive disease) was dependent on the treatments tested, and was statistically significant ($P < 0.01$, Chi-squared test). Figure 2 shows the means and 95% confidence intervals (CI) of the percentage increase in tumor size after treatment in the three groups. Increases in tumor size were significantly lower in patients treated with insulin + methotrexate than in those treated with insulin alone and significantly lower than in those treated with methotrexate alone. From the same set of measurements, Figs. 1 and 2 show the clinical and biological effects of the treatments, respectively. Figure 1 indicates that the decrease in tumor growth induced by insulin + methotrexate reached the level of a clinically confirmed antitumoral response because more patients in this group achieved stable disease. Figure 2 shows that insulin + methotrexate treatment reduced tumor growth. All patients completed the study. The best response obtained, was in the group treated with insulin + methotrexate malignant cells is attributed to

Conclusion

The in vitro potentiation of methotrexate cytotoxicity by insulin in human breast cancer cell lines was previously known. We report the results of a randomized, controlled trial that confirmed, at the clinical level, the potentiation by insulin of the antitumoral effect of methotrexate in women with advanced breast cancer. Under the conditions of this study, the dose of insulin used did not increase tumor growth.

Breast Cancer Survivor

1997 – The year I learned that I had mastectomized breast cancer – stage 2, type B – meaning it was fairly large, was still treatable, and had spread to the lymph node some-time ago. The treatment was through UCLA Medical Center as a clinical trial – which meant stronger dosages to try to prevent the return of the cancer. I was told that without the treatment the best prognosis was 70% chance of cancer again within 5 years, but with the treatment 70% chance of no cancer. I chose the clinical trial because (1) I felt I already was “to die” and (2) I might help some other young woman with a gift of a cure. I ended up having 5 surgical procedures – including putting in the “port” and I was weak, almost not “alive”, and very afraid of the chemo. Chemo was not so bad, but still, I lost every bit of hair everywhere, sometimes my eyes teared with caustic fluids so I wore eye patches; I hurt, I could not sleep because I was “wired” with chemo, and I had mouth sores, and all the other yucky stuff that was stated in the papers I had to sign. Most often I could barely eat a bite or two of mashed potatoes or jello.

BUT I had something more many do not have. I had God and people praying around the world for me! I had so

many people praying that when I went into the operating room for the first surgery I didn't think the gurney would fit through the doors because the “Presence” was so large around me.

I have a wonderful husband who would NOT let me stop living, and I remember after one chemo treatment flying to Ohio where I laid on the floor in the airport and talked to people because I had to get my tummy and legs “flat”. And, I had been taking vitamins and supplements regularly before and during chemo [after the first 3 days after a treatment]. I also listened to two Kenneth Copeland CD's: Healing Praise and Peaceful Praise at least 2-3 or more times a day. This not only became my confession, but also grew my faith! In fact, a nurse said I didn't look like someone going through chemo and what was my secret? I told her about the above.

After 3 months, I started to become more “normal”, but suffered from Pneumonia and Bronchial Attacks 3-4 times in 1998. Then, when Omega 3's became known to me, I did an enormous recovery in a year! There truly is healing powers from God in Omega 3!



About the same time, unknown to me, my heart was having arrhythmia – irregular heart beats, that were keeping me from getting enough oxygen to my heart and other organs. In 2003 I was finally so bad that after Christmas in Phoenix, AZ area I called 911 and was taken to Osborn Medical Center in Scottsdale, AZ. I did not know that this was the very best place for me nor that my doctor was the best one for me until later. I ended up with a pacemaker and defibrillator because my heart was not stable so able to keep me alive. After about a year of trying doctor after doctor (because I was deathly ill daily), I finally found out about Dr. David Korn through my church. The staff at Long Life Medical treated me like I was family, and would not let me settle for “a little better”. Since then I have had one more heart failure [one heart medicine stopped working], and I thought I had a bad “bug”. But after that, Dr. Korn put me on L-carnitine along with B-Ribose and the high doses of CoQ10 and Omega 3 that I was already taking. I am very happy to tell you this is the first Christmas season that I stayed well since 1997. I have renewed strength, and no longer take a nap every day. I thank God for Dr. Korn and his staff for I know that they have helped me back to a full life again. I'm now 68 and cannot run with my 5-year-old grandson, but I can lift him and play games with him and teach him about Jesus and about being good. Life is good!
 Marci Crabtree

HER2 Breast Cancer Testing

Women who are uncertain of their cancer's HER2 status should talk to their doctor. HER2+ breast cancer is often more aggressive, so it is important to find out your cancer's HER2 status. This can help your doctor choose which treatments may be right for you.

HER2 testing is performed with the tumor sample removed during surgery or using a needle.

There are 2 types of tests available to determine HER2 status: Fluorescence In Situ Hybridization (FISH) and ImmunoHistoChemistry (IHC).

A FISH test checks to see whether or not the cancer cells have a normal number of [HER2 genes](#). Using a special microscope the [pathologist](#) looks at cancer cells to see how many HER2 genes there are compared with some other normal genes

- If there are 2 or more HER2 genes for each normal gene in the cells (that is, if the ratio is =2.0) the tumor is HER2+

An IHC test measures how much [HER2 protein](#) there is on the surface of the cancer cells. The test is scored on a scale of 0 to 3+

- A patient who has a tumor with a score of 3+ is considered to have HER2+ breast cancer
- The National Comprehensive Cancer Network guidelines recommend that a tumor with a score of 2+ should be retested with the FISH test to determine whether the tumor is HER2+

Accurate testing is important; your pathology report may contain inconclusive results.

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