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Inositol hexaphosphate (InsP6) as an effective topical treatment for patients receiving adjuvant chemotherapy after breast surgery

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Abstract. – OBJECTIVE: Oral treatment with inositol hexaphosphate ($InsP_6$) has shown to be efficient in decreasing adverse effects in patients with breast cancer under chemotherapy. This study was aimed at evaluating and comparing the efficacy of topical $InsP_6$ in improving quality of life in women treated with anticancer drugs.

PATIENTS AND METHODS: The study was a double-blind, randomized controlled trial (RCT) with allocation concealment of 20 patients in two groups, one (experimental) applied 4% topical formulation of $InsP_6$ once a day, whereas the second one (control) a gel containing hyaluronic acid. $InsP_6$ therapy started 6 weeks after lumpectomy. Blood tests were monitored in both groups and quality of life was assessed using standardized QLQ-C30 and QLQ-BR23.

RESULTS: Patients who applied $InsP_6$ on the breast significantly improved their quality of life and functional status reducing side effects compared to control group; moreover, after treatment, a significant difference between the two groups was observed in the white blood cells and platelets count values.

CONCLUSIONS: Topical $InsP_6$ treatment has demonstrated to be effective and safe in preventing and/or mitigating chemotherapy-induced side effects as well as the preserving quality of life in women with ductal breast cancer.

Key Words:
Inositol hexaphosphate, Chemotherapy, Phytic acid, Phytate, $InsP_6$, IP_6, Breast cancer.

Introduction

Breast cancer is by far the most common malignant tumor in women worldwide, with 1.7 million new cases and 522.000 deaths in 2012[1]. Since 2008, breast cancer incidence has increased by more than 20%, whereas mortality has increased by 14%. In more developed countries incidence rates remain quite high, but mortality is relatively much higher in less developed countries due to a lack of early diagnosis and access to treatment facilities[2]. Currently, there is not sufficient knowledge available on the causes of breast cancer; therefore, early diagnosis of the disease remains the cornerstone of breast cancer prevention and control.

Different therapeutic strategies may be adopted in women diagnosed with breast cancer, depending on type and stage, before or after surgery: chemotherapy, radiation therapy, hormone therapy. However, these treatments can be quite aggressive, depending on the specific agents used in the adjuvant regimen as well as on the dose used and the duration of treatment, causing adverse effects defined as short- or long-term side effects: short-term like nausea, vomiting, weight loss, fever, diarrhoea, reduction of blood cell count values and long-term side effects such as hair loss, insomnia, depression, chronic pain, fatigue, anxiety, organ damage, cognitive impairment and

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problems related to affective and sexual sphere. In 10% of cases, these upsets cause the interruption of treatment cycles[3]. In particular, short-term side effects, which heavily impact on quality of life, may also impair chemotherapy. Indeed, they may lead to postpone or discontinue a treatment cycle. This suspension exposes patients to the risk of distant metastasis occurrence, reducing the chance for a complete recovery. Although recently, medical advances have significantly improved the survival of many cancer sufferers, a large number of them are still affected by the various heavy side effects (like anaemia, nausea, vomiting, immune dysfunction, and asthenia). Therefore, not only the life span, but also the quality of life, is playing a growing key role in the approach to a cancer patient. Clearly today the objective of oncologists is not only the enhancement of survivors by decreasing disease severity, but also the search for clinical benefits to patient's quality of life. The minimization of the adverse effects related to tumor progression and oncotherapy promotes a better quality of life and, therefore, it is crucial to dwell on this critical aspect for cancer patients[4].

Inositol hexaphosphate ($InsP_6$, phytic acid), is a naturally occurring component in almost all plants, and can be detected at high concentrations in cereals, legumes, seeds, nuts, and mammalian cells[5]. It is well known that this molecule plays a compelling role in ensuring the proper function of a plethora of key cellular processes. Its strong activity as antioxidant is due to the phosphate groups in positions 1, 2, and 3. Such spatial shape can be found only in $InsP_6$, and it gives a specific interaction with iron to completely block its ability to catalyse hydroxyl radical formation. Several experimental models have demonstrated its antioxidant action as scavenger of free radicals[6-8]. $InsP_6$ was shown to be involved in a number of cellular functions, such as effects on ion channels and protein trafficking[9,10], exocytosis[11], endocytosis[12], oocyte maturation[13], cell division and differentiation[14], DNA repair[15,16], and protein folding[17].

Many $InsP_6$ beneficial effects for human health have been described, such as striking anticancer function, strengthening the body's immune system, inhibition of pathological calcification, and reduction of serum lipid levels[18-22]. Furthermore, orally administered $InsP_6$, eventually in combination with inositol, during chemotherapy, has been shown to significantly reduce the side effects and ameliorate the quality of life in patients with a number of different cancer types, such as breast, colon and lung cancer[23-28]. Grases et al[29,30] have investigated the pharmacodynamics and pharmacokinetics of $InsP_6$. Studies on the pharmacokinetic of $InsP_6$ in oral form have shown that its absorption is carried out in a quantitative way, but it is significantly influenced by calcium concentrations in the diet[31,32] and by the eventual pre-existing $InsP_6$-depleted deposits in tissues, which can lead to an aleatory absorption[33]. In particular, the complexation of phytic acid in the intestinal tract can greatly limit its absorption. Besides, topical $InsP_6$ administration was seen to allow high absorption levels, overcoming the limits of its oral administration[34-35].

Based on this clinical evidence and on the need for improving the quality of life in cancer patients, we carried out a double-blind, randomized controlled trial (RCT) to evaluate the benefits of topical $InsP_6$ used in women with ductal breast cancer undergoing cycles of postoperative chemotherapy.

Patients and Methods

A double-blind, RCT was conducted, with allocation concealment. The inclusion criteria were patient's age between 26 and 76 years, with ductal breast cancer stage II-III, postoperative (lumpectomy). On the other hand, women who have undergone mastectomy were excluded from the study. At recruitment, a descriptive analysis of general and clinical characteristics was performed interviewing each patient. The trial was conducted in an outpatient unit and all patients filled an informed consent. This study was approved by the ethics committee of the Italian Society of Phytotherapy and Supplements in Obstetrics and Gynecology (SIFIOG).

Twenty-seven women were assessed for eligibility and twenty were enrolled, between February 2014 and October 2015. The 7 patients excluded from the study were undergoing neoadjuvant chemotherapy. Patients in both arms received the same polychemotherapy CMF (cyclophosphamide, methotrexate and 5-fluorouracil), for a total of six cycles. The enrolled women were divided into two groups, according to a block randomization model[36]; one experimental group ($InsP_6$ group) and one control group (hyaluronic acid). To ensure a correct balance between the two groups, patients were randomized to treatment using a minimization procedure[37] and according to such model the sample size should exceed eight units in each arm. The $InsP_6$ group consisted of 10 women, undergoing polychemotherapy, treated

with 5 g of 4% topical $InsP_6$ as sodium salt (corresponding to 200 mg of $InsP_6$), applied on the operated breast once a day. The control group consisted of 10 women treated chemotherapeutically, combined with 5 g of a gel containing hyaluronic acid. Women were instructed to apply the topical treatments on the operated breast for 6 months. The treatments application started 6 weeks after lumpectomy. Physicians recorded patients' compliance during scheduled medical visits. The primary outcome was the evaluation of the quality of life and chemotherapy-induced side effects.

Blood samples were taken from each group and analyzed; the results were assessed as a secondary outcome of the study (white blood cells, platelets, red blood cells and hemoglobin). The appearance of any side effects, as well as the presence of other changes in clinical and laboratory parameters (ALT, LDH, AST, AP, creatinine, bilirubin, electrolytes and urea) has been accurately recorded.

Clinical Scores and Statistical Analysis

The primary outcome was the evaluation of the effectiveness of topical $InsP_6$ therapy, in improving the quality of life and reducing side effects in women undergoing polychemotherapy for breast cancer (after lumpectomy). To assess this parameter, all 20 patients filled in the questionnaires QLQ-C30 and QLQ-BR23 of the 'European organization for testing the treatment of cancer (EORTC)' guideline, at the beginning and at the end of treatment with $InsP_6$. The questionnaire QLQ-C30 is based on measuring breast cancer-specific quality of life and consists of five scales each composed of several questions that assess physical, role, cognitive, emotional and social functioning. The specific module QLQ-BR23 consists of multiple questions to evaluate the side effects of systemic therapy.

Adverse effects, occurring after chemotherapy, are divided into subjective and objective symptoms: fatigue, nausea and vomiting, hair loss, constipation, diarrhea and abdominal pain, musculoskeletal pain, decreased appetite, changes in the skin (hyperpigmentation or peeling on the skin or nails), allergic reactions, neurological disorders (such as tingling and itching in hands and feet), difficulty in moving, changes in menstrual cycle (with possible early menopause) and cardiac dysfunction.

All items were scored on 4-point Likert scale, which measures all scales and individual statements with a percentage score from 0 to 100. QLQ-C30 SC was used for processing the data obtained from the questionnaires.

The results were tested for significance by means of Student's t-test for small samples, and the value of $p \leq 0.05$ was considered significant. All values are shown as mean ± SD.

Results

All 20 patients involved followed the protocol and any dropout over the trial period was recorded. At the end of six months treatment, quality of life was assessed using standardized questionnaires QLQ-C30 and QLQ-BR23. Topical treatment either with $InsP_6$ or hyaluronic acid was regularly applied by the patients, belonging to experimental and control group respectively, during the study period. Baseline clinical characteristics of patients were well balanced between treatment arms.

The results (Table I) showed that topical $InsP_6$ is able to significantly improve the quality of life in women with breast cancer undergoing polychemotherapy, with the average score of 80.5 ± 15.0 in treated group and 40.4 ± 25.0 in control group ($p \leq 0.001$). The functional status resulted, from the answers to questionnaires, in an average score of 88.9 ± 22.0 in the experimental group compared to 51.6 ± 23.0 in the control group ($p \leq 0.001$), demonstrating that subjects treated with $InsP_6$ were able to perform normal daily activities and maintain a satisfactory well-being.

Clinical symptoms of side effects caused by chemotherapy significantly dropped down in $InsP_6$ group (average score 12 ± 10) compared to control (average score 45.81 ± 10.0) ($p \leq$

Table I. Results obtained from the standardized questionnaires QLQ-C30 and QLQ-BR23. Values are shown as mean ± SD.

	Control group Mean ± SD	InsP6 group Mean ± SD	*p*-value
Quality of life	40.4 ± 25.0	80.5 ± 15.0	≤0.001
Functional status	51.6 ± 23.0	88.9 ± 22.0	≤0.001
Clinical symptoms of side effects of therapy	45.81 ± 10.0	12.0 ± 10.0	≤0.001
Cycles postponed	37.5%	12.5%	-

0.001). Also, the postponed cycles of chemotherapy were three times lower in the treated group where only 12.5% of postponed cycles occurred, compared to the control group that showed a percentage of 37.5%.

In addition, complete blood cells count showed that the number of white blood cell (WBC) before treatment was 7.35 ± 2.5 x 10^9/L in treated group and 7.5 ± 2.5 x 10^9/L in control group. After treatment WBC remained at normal values in the $InsP_6$ patients (6.85 ± 1.3 x 10^9/L), whereas it decreased drastically in control group (2.7 ± 1.5 x 10^9/L) (Figure 1). Moreover, in the $InsP_6$ group the platelets counts were 285.12 ± 95.0 x 10^9/L before treatment and 268.98 ± 53.0 x10^9/L after treatment, whereas in control group decreased significantly after treatment resulting in a mean value of 115.32 ± 52.0 x 10^9/L compared to 280.80 ± 81.0 x 10^9/L before treatment (Figure 2).

Furthermore, as reported in Table II, there were no significant changes in the count of red blood cells (RBC) showing prior treatment a mean value of 4.36 ± 3.0 x 10^{12}/L in the experimental group and 4.30 ± 2.5 x 10^{12}/L in the control group. RBC values after treatment were 4.28 ± 1.4 x 10^{12}/L and 4.1 ± 3.5 x 10^{12}/L, respectively.

The hemoglobin level before treatment was 12.5 ± 4.7 g/100 mL in the treated group and 12.2 ± 4.7 g/100 mL in the control group. After treatment, no changes were recorded in the $InsP_6$ patients. Among them the average was 12.8 ± 9.0 g/100 mL, whereas in control group the hemoglobin levels resulted slightly reduced, but not significantly (11.2 ± 3.9 g/100 mL) (Table II).

The parameters such as ALT, LDH, AST, AP, creatinine, bilirubin, electrolytes and urea monitored during the treatment were stable in both groups (data not shown).

Discussion

In this clinical study, we have shown that topical use of a formulation containing 4% phytic acid was effective in improving the quality of life and reducing the side effects of chemotherapy in women with breast cancer. In addition, $InsP_6$ group had only 12.5% of postponed cycles over all the treatment period, three times less compared to control group. Besides, a significant difference was observed between treated and control groups in the WBC and platelets count values after treatment.

The polyphosphorylated carbohydrate $InsP_6$, contained in substantial amounts in almost all plants and mammalian cells, is one of the strongest antioxidant found in nature. Its characteristic conformation provides a specific interaction with iron, in this way inhibiting the iron ability to catalyze hydroxyl radical formation. Its action was documented in several experimental models in vivo[38], including myocardial reperfusion injury[6], lung inflammation[7], inflammation and ulcer induction[8]. The beneficial effects of $InsP_6$ on strengthening the immune system and lowering serum cholesterol are well known for a long time[39-41]. In addition, $InsP_6$ showed a significant antitumor effect against different types of experimental cancer[40,42]. Since 1998, clinical studies

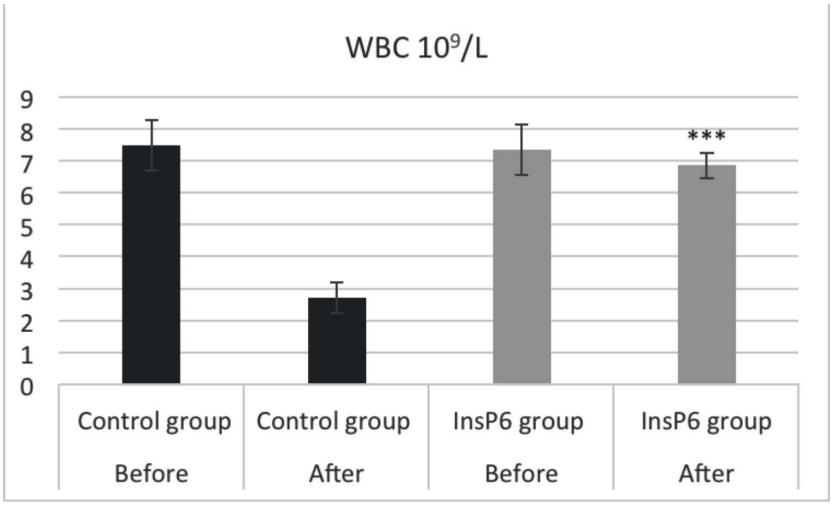

Figure 1. Results of white blood cell count. A statistically significant difference ($p \leq 0.001$) was found between the two groups after treatment. Values are shown as mean ± SD.

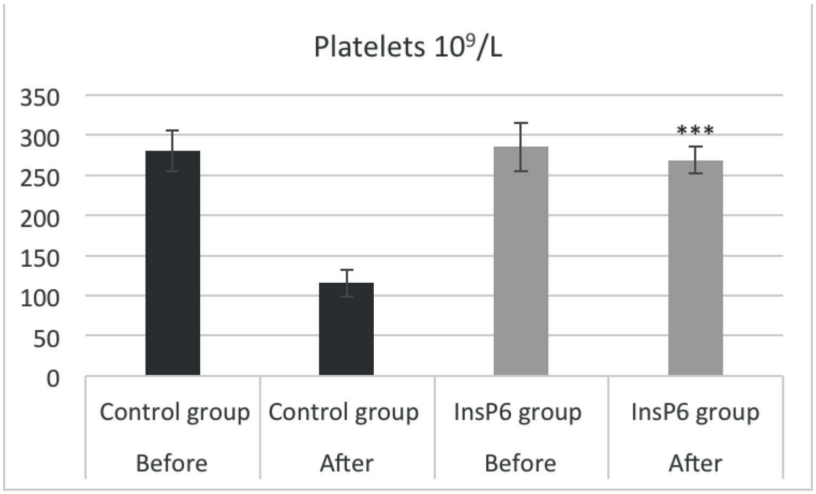

Figure 2. Results of platelets count. A statistically significant difference ($p \leq 0.001$) was found between the two groups after treatment. Values are shown as mean ± SD.

have confirmed the broad-spectrum anti-cancer activity in humans. $InsP_6$ inhibits the major pathways of malignancy, such as proliferation, cell cycle progression, metastasis, angiogenesis, apoptosis[43,44] and differentiation[45-48].

In a number of clinical trials, it was reported that, when $InsP_6$ was given orally in combination with chemotherapy, side effects correlated to the oncotherapy for colon cancer were diminished, therefore improving patient's quality of life and maintaining the chemotherapy regimen[23,24]. Additionally, oral $InsP_6$ treatment, as an adjuvant to chemotherapy, has demonstrated to improve the quality of life and long-term survival in patients with breast cancer[25-27] and advanced lung cancer[28].

These clinical studies provided very encouraging results considering that in a cancer patient quality of life and adverse effects imply a very critical aspect during the oncological treatment, and have to be taken in deep consideration. For this reason, the European Association for Research and Treatment of Cancer (EORTC) has developed questionnaires for assessing the quality of life in patients undergoing chemo- or radiotherapy. Our clinical study aimed at evaluating the topical use of $InsP_6$ in women with ductal breast cancer undergoing cycles of postoperative chemotherapy and the consequent outcomes regarding their quality of life utilizing the questionnaires QLQ-C30 and QLQ-BR23 from the EORTC, with a substantial interest for the values of complete blood cells count.

The data collected from the questionnaires used in this study show that the frequency and intensity of side effects were significantly decreased in the treated group compared to the control group. This effect can be explained by the antioxidant activity of $InsP_6$[49]. It is well known that chemotherapy drugs are most responsible for the onset of nausea and vomiting, due to the stimulation of the vomiting center, in particular, the trigger zone, and the gastrointestinal tract. Antioxidants exert a

Table II. Change in Complete Blood Cell Count Values. A significant difference was observed between the 2 groups after treatment in the WBC and platelets count values. There was no statistical difference between groups in the levels of RBC and hemoglobin. Values are shown as mean ± SD.

	Control group Mean ± SD		$InsP_6$ group Mean ± SD		
	Before	After	Before	After	*p*-value
WBC 10^9/L	7.5 ± 2.5	2.7 ± 1.5	7.35 ± 2.5	6.85 ± 1.3	≤0.001
Platelets 10^9/L	280.8 ± 81.0	115.32 ± 52.0	285.12 ± 95	268.98 ± 53.0	≤0.001
RBC 10^{12}/L	4.3 ± 2.5	4.1 ± 3.5	4.36 ± 3.0	4.28 ± 1.4	NS
Hemoglobin g/100mL	12.2 ± 4.7	11.2 ± 3.9	12.5 ± 4.7	12.8 ± 9.0	NS

mucus-protective action on them, which not only has the ability to calm and soothe the gastric mucosa, but also to protect cells from free radicals, both at the gastric level and on the nervous system, therefore reducing the chemotherapy adverse effects, such as nausea and vomiting[50]. Moreover, analyzing the answers from the questionnaire QLQ-C30 emerged, as expected, that quality of life was much better in patients treated with $InsP_6$ than in control patients.

Monitoring of complete blood counts was conducted on all patients throughout treatment, forasmuch as anomalies in the blood panel values are often seen in patients receiving chemotherapy. Precisely, chemotherapy medicines damage the bone marrow, causing consequently a lower production of RBC, WBC and platelets. Typically, the greatest impact is on WBC making patients more vulnerable to infection. Changes in the complete blood cells count and especially low levels of WBC induce the oncologist to postpone the chemotherapy cycles in order to prevent any additional undesirable clinical condition on patient undergoing oncotherapy. For this reason, the maintenance of normal blood cells values during treatment is a paramount aspect for guarantee regularity to chemotherapy cycles and avoids delays or even interruption of therapy[51].

In this clinical study, the erythrocytes and hemoglobin levels stayed on normal values and no significant difference was recorded between the two groups, either before or after treatment. However, treatment with $InsP_6$ prevented the excessive reduction of WBC and platelets allowing patients to adhere fully to the chemotherapy protocols with no need to postpone some cycles (Table II). Only the 12.5% of chemotherapy cycles was postponed in the $InsP_6$ group compared to control in which the number of cycles postponed was tripled. Ultimately, taking into account the small number of cycles delayed, we can say that the topical administration of $InsP_6$ increases the effectiveness of chemotherapy.

Overall, this clinical investigation draws attention to the topical use of $InsP_6$ for reducing the side effects and improving the quality of life of post-operative breast cancer patients undergoing chemotherapy.

Conclusions

Despite the clinical study has been conducted on a small number of patients, the results highlight the beneficial effect of $InsP_6$ as an adjuvant of chemotherapy for breast cancer and the improvement in patients' quality of life. Anyway, it would be useful to conduct further studies and clinical trials on a larger number of patients with breast cancer for further evaluations, in order to assess different concentration or treatment duration and learn even more on the impact that $InsP_6$ could have once administered topically. It was seen that this molecule taken orally is effective in a number of cancer types[25-28,47-48], although this way of administration implies some limits. Therefore, it would be worthy to extend the clinical trials to other kinds of oncological pathologies and determine whether the same positive effects on quality of life would be observed with topical administration of $InsP_6$.

Conflicts of interest

The authors declare no conflicts of interest.

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