NUTRITION AND CANCER, *58*(1), 43–48

Wheat Grass Juice May Improve Hematological Toxicity Related to Chemotherapy in Breast Cancer Patients: A Pilot Study

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Abstract: *Myelotoxicity induced by chemotherapy may become life-threatening. Neutropenia may be prevented by granulocyte colony-stimulating factors (GCSF), and epoetin may prevent anemia, but both cause substantial side effects and increased costs. According to non-established data, wheat grass juice (WGJ) may prevent myelotoxicity when applied with chemotherapy. In this prospective matched control study, 60 patients with breast carcinoma on chemotherapy were enrolled and assigned to an intervention or control arm. Those in the intervention arm (A) were given 60 cc of WGJ orally daily during the first three cycles of chemotherapy, while those in the control arm (B) received only regular supportive therapy. Premature termination of treatment, dose reduction, and starting GCSF or epoetin were considered as "censoring events." Response rate to chemotherapy was calculated in patients with evaluable disease. Analysis of the results showed that five censoring events occurred in Arm A and 15 in Arm B (*$P = 0.01$*). Of the 15 events in Arm B, 11 were related to hematological events. No reduction in response rate was observed in patients who could be assessed for response. Side effects related to WGJ were minimal, including worsening of nausea in six patients, causing cessation of WGJ intake. In conclusion, it was found that WGJ taken during FAC chemotherapy may reduce myelotoxicity, dose reductions, and need for GCSF support, without diminishing efficacy of chemotherapy. These preliminary results need confirmation in a phase III study.*

Introduction

Hematological toxicity is one of the main side effects of chemotherapy treatment and occasionally the cause of life-threatening toxicity. Although the standard treatment for neutropenia is administration of granulocyte colony-stimulating factors (GCSF), the routine use of GCSF for primary prophylaxis with any chemotherapy cannot be justified on the basis of cost effectiveness (1). According to ASCO guidelines, GCSF as primary prophylaxis is recommended when available data indicate an incidence of febrile neutropenia exceeding 40%. The administration of GCSF reduces hospitalization for antibiotic administration (1).

The development of chemotherapy-associated anemia is characteristically an insidious and delayed complication of treatment, and becomes clinically more significant when a combination of drugs is administered (2). The use of epoetin is recommended for patients with chemotherapy-associated anemia if the hemoglobin concentration decreases below a level of 10 g/dL. Red blood cells transfusion is also a therapeutic option, depending upon the severity of anemia or clinical circumstances (2).

Both GCSF and epoetin cause substantial side effects and increase expense, thus precluding their use on a regular basis. Finding ways to reduce myelotoxicity without additional side effects and at a reasonable cost may improve quality of life and attain dose densities. Wheat grass juice (WGJ) is an extract squeezed from the mature sprouts of wheat seeds (Triticum aestivum). The use of WGJ for therapeutic purposes was developed and popularized by Dr. Ann Wigmore (1909–1996), as part of her therapeutic nutritional approach (3). The therapeutic qualities of WGJ have been attributed to its rich nutritional content, including chlorophyll, vitamins (A, C, and E), bioflavonoids, iron, minerals (calcium and magnesium), and 17 amino acids, 8 of which are essential (4). Tables 1 and 2 contain the detailed nutritional content of WGJ grown in Israel, as studied by Israeli laboratories (The Center for Food Research and Development, Technion-Israel Institute of Technology, Haifa, and Aminolab, Weitzman Institute, Rehovot) (5). Although proponents of WGJ have recommended it for four decades as a treatment for various illnesses, very little clinical data exist to support its use. WGJ was found to reduce symptoms in patients with rheumatoid arthritis (6), to reduce severity of rectal bleeding in patients with ulcerative colitis (7), and to reduce the frequency of blood transfusions in patients with thalassemia major (8). The use of WGJ in an attempt to reduce chemotherapy-induced hematological toxicity in cancer

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Table 1. Levels of Vitamins and Minerals in 100 Ml of Wheat Grass Juice

Vitamins & minerals	Amount (mg/100 ml)
Ascorbic acid	25.2
Dehydro ascorbic acid	7.6
Vitamin E	8.5
Carotene	2.43
Potassium	57
Phosphorus	8.2
Calcium	2.4
Sulfur	2.37
Magnesium	1.7
Sodium	1.42
Aluminum	0.31
Zinc	0.02
Copper	0.007

(Copied with permission from Dr. Pnina Bar-Sella, Ref. 5).

Table 2. The Contents of Amino Acids in Wheat Grass Juice

Amino acid	Amount (μg/ml)
Aspartic acid	510.3
Threonine	105.8
Serine	201.8
Asparagine	3039.6
Glutamine	200.6
Proline	33.6
Glycine	20.6
Alanin	166.4
Valine	272.1
Methionine	14.0
Isoleucine	145.1
Leucine	101.0
Tyrosine	121.8
Phenylalanine	200.9
Lysine	174.5
Histidine	232.2
Tryptophan	160.1
Arginine	252.9

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patients was brought to our attention by patients. In a comprehensive search of the literature, we could not find any support for this approach for chemotherapy-induced toxicities.

FAC combination (5-fluorouracil, doxorubicin, and cyclophospamide) is a well-established chemotherapy regimen frequently used in the treatment of breast cancer patients. The FAC regimen induces grade 3 and 4 leucopenia in about 65% of patients, necessitating hospitalization in 5% (9). The regular use of GCSF for primary prevention with this regimen is usually not recommended (1).

The purpose of the present prospective, matched pair pilot study was to determine whether WGJ can reduce the incidence of chemotherapy-related myelotoxicity in breast cancer patients.

Patients and Methods

Study Design

The study was conducted in accordance with Helsinki procedures and was approved by the local research ethics committee. All patients provided written informed consent. Women aged >18 yr, diagnosed with histologically proven invasive breast carcinoma who had not received any prior chemotherapy were enrolled. All patients except one were enrolled to the study at initial diagnosis. Other eligibility criteria included WHO performance status 0–2 and clinical or pathological tumor stage I–IV. Patients intending to receive primary prophylactic GCSF, who planned to use any wheat juice products, or were on warfarin treatment during chemotherapy were excluded from the study.

All patients were intended to receive the FAC regimen by their referring physicians. According to the policy at our hospital, doses in the adjuvant or preoperative setting are 600/60/600 mg/m^2, respectively, and 500/50/500 mg/m^2, respectively, in patients with stage IV disease. The treatment is repeated every 21 days.

Treatment

Patients were prospectively assigned by a matched pair design to either an intervention or control arm, according to age, disease stage, and blood count assessed before starting the first cycle of chemotherapy. Each patient in the intervention arm (arm A) was supplied with frozen wheat grass juice divided into daily doses of 60 cc. Patients were asked to drink one dose every morning on an empty stomach. This intervention continued for the first 3 cycles. According to the protocol, it was allowed to delay the intake of WGJ by 1–3 days following each chemotherapy cycle if the patient felt nausea. Patients in the control arm (arm B) received no supplement besides regular supportive treatment.

Blood samples for complete blood counts were taken on day 1 of each cycle and at weekly intervals. The nadir results in every cycle were recorded.

Premature termination of treatment, dose reduction, or starting treatment with GCSF or epoetin was each considered a censoring event. The primary end point of the study was comparing the incidence of any censoring event in both arms. A secondary end point was determining the influence of WGJ intake on hemoglobin levels, so patients who started GCSF treatment continued to be followed for hemoglobin levels until the end of the 3rd cycle. Patients with evaluable disease during treatment, including those receiving preoperative therapy and those with stage IV disease, were also assessed for response to chemotherapy.

Statistical Analysis

The matched control technique was applied prospectively on the basis of patient age, stage of disease, and pretreatment blood count. Each newly enrolled patient was matched with a previously treated patient with comparable details and

Table 3. Characteristics of Patients at the Time of Enrollment in the Study

Characteristic	Arm A ($N = 30$)	Arm B ($N = 30$)
Age–median (range)	53 yr (32–65)	49 yr (26–68)
Stage		
– I	5	6
– II	17	18
– III	5	3
– IV	3	3
Blood count: median (range)		
– White blood cells (cells/mm^3)	6,900 (4,500–10,600)	7,300 (4,800–15,000)
– Neutrophils (cells/mm^3)	3,900 (1,900–7,000)	4,350 (2,300–10,300)
Platelets (cells/mm^3)	265,500 (141,000–384,000)	259,500 (130,000–635,000)
– Hemoglobin level (g/dL)	12.9 (10.8–16.1)	13.05 (11.2–14.6)

assigned to the opposite arm accordingly or, if no matched case was found, was assigned randomly and a matched case was enrolled later. This rule was violated only in two patients in whom arm selection was made according to patient's request.

Data were analyzed using the SPSS 12.0 software. Association between categorical groups was analyzed using the Chi square test or Fisher's exact test as appropriate. Comparison between continuous variables was done with the Mann-Whitney U test. Two-tailed P values of 0.05 or less were considered as statistically significant.

Results

Between February 2003 and March 2005, 60 patients were enrolled in the study, 30 patients in each arm. Median age was 50 yr (range, 26–68 yr). Six (10%) patients, three in each arm, received reduced doses of the FAC regimen (500/50/500 mg/m^2, respectively) due to stage IV disease. Five of these patients were diagnosed with systemic spread on the initial presentation of their disease, while one patient had recurrent disease but had not received prior chemotherapy. Ten patients (five in each arm) were treated in a preoperative setting due to advanced loco-regional disease. All patients had a performance status of 0–1. The two arms were well balanced with regard to treatment characteristics and pretreatment blood counts, as summarized in Table 3.

Primary End Point Results

In arm B, 15 (50%) censoring events occurred, 11 (37%) of which were of a hematological nature. In arm A, a total of 5 (17%) censoring events were recorded, all caused by hematological toxicity. The differences between the two groups were statistically significant, both for all toxicities (odds ratio 5.0, 95% CI 1.5–16.6, $P = 0.013$) and particularly for hematological events (odds ratio 3.7, 95% CI 1.07–12.6 $P = 0.043$). The main causes of the 'censoring events' are summarized in Table 4.

Table 4. Incidence of 'Censoring Events' According to Study Definition

Event	Arm A (no. of pts)	Arm B (no. of pts)
Neutropenic fever	3	5
Leucopenia with infection	0	3
Prolonged neutropenia (on day 21)	2	3
Non-hematological toxicity	0	3
Tumor progression	0	1

Two patients in arm B stopped chemotherapy prematurely (one with stage IV disease, due to tumor progression following the 2nd cycle, and the other due to uncontrolled high blood pressure after the 1st cycle). Two other patients in arm B required dose reductions of chemotherapy due to non-hematological toxicities: one had grade 3 stomatitis and the other suffered from grade 3 fatigue. No non-hematological censoring events were observed in arm A.

Influence of WGJ on Blood Counts

At enrollment into the study, all patients had normal blood counts with no significant differences between the two arms (Table 3). Following the first chemotherapy cycle, 5 (17%) patients in arm A and 13 (43%) patients in arm B developed grade 3 or 4 leucopenia ($P = 0.047$). No significant difference between arms was observed in the neutrophil count; 23 (77%) patients in arm A and 28 (93%) patients in arm B had grade 3 or 4 neutropenia. This discrepancy in comparison of white blood cells between the two arms is due to a relative lymphocytosis in arm A.

The majority of hematological censoring events occurred following the 1st chemotherapy cycle, three in arm A and eight in arm B. Three patients in arm A and five in arm B developed neutropenic fever which required hospitalization for administration of intravenous antibiotics. Bacterial infection was found in three patients in arm B, but none in arm A. Prolonged neutropenia causing delay in the following cycle was observed in two patients in arm A and in three patients in arm B.

Hemoglobin levels at the end of the study defined as the nadir following the 3rd cycle showed a median reduction of 1.2 g/dL in arm A, calculated for all 30 patients, and a median reduction of 1.9 g/dL in arm B calculated for the 22 patients who succeeded in completing three cycles without dose reductions ($P = 0.025$).

No grade 3 anemia was observed. Four patients, two in each arm, developed anemia with hemoglobin levels of less than 10 gr/dL; nevertheless, none received epoetin according to the decision of their physicians. Thrombocytopeniagrade

1 occurred in two patients in arm A and one patient in arm B. Using the Mann-Whitney U test, we could not find any pretreatment characteristic which would predict the development of a censoring event during treatment.

Response to Chemotherapy

Forty-four patients received the CAF regimen as adjuvant therapy and thus were not evaluable for response; also, follow-up was too short to compare survival rates between the two arms. The remaining 16 patients, 8 in each group, were evaluable for tumor response. They included 6 patients with stage IV disease and 10 with locally advanced disease, evenly divided between the two arms. No significant difference in response rate was found between the two groups: In arm A, 6/8 (75%) patients had a partial response to treatment (3 with stage IV disease and 3 in the preoperative group). In arm B, 5/8 (63%) patients achieved response to the treatment (2 with stage IV and 2 in the preoperative treatment group had partial response, while one patient with locally advanced disease had complete clinical remission). Time to tumor progression (TTP) was as follows: 5, 8, and 10 mo in 3 patients with stage IV disease treated with WGJ, and 2, 2, and 4 mo in 3 stage IV patients in the control arm. In a median follow-up of 54 non-metastatic patients, there were 2 recurrences in each arm (2/27; 7.4%), these recurrences came after 13–18 months from entering the study. Median follow-up duration for these patients was 23 mo.

Toxicity

Side effects related to WGJ intake were minimal, 73% of patients (22/30) reported difficulties in swallowing the juice due to its strong grass-like taste. Six (20%) patients failed to complete 10 wk of intake of the WGJ due to worsening of nausea.

Discussion

This pilot matched control study demonstrates a statistically significant reduction in the rate of chemotherapy-induced toxicity (17% versus 47%, $P = 0.01$) as a result of the daily intake of WGJ during therapy with FAC combination in patients with breast cancer. No compromise in the antineoplastic efficacy of the chemotherapy was observed along with the reduction in toxicity.

The effect of WGJ was most profound with regard to hematological toxicity (17% versus 37%, $P = 0.04$). The most important effect observed was a reduction in neutropenic fever events and in neutropenic infections. Similar results were reported in a pilot study in which 22 patients (11 pairs) with solid pediatric malignancies were enrolled to either a treatment arm with a fermented wheat germ extract (medical nutriment MSC-Avemar) or to a control arm. A reduction in chemotherapy-induced neutropenic fever events from 43.3% to 24.8 % was observed (10).

In the current study, a significant reduction in grade 3 or 4 leucopenia (17% versus 43%) was observed in the intervention group, following the first chemotherapy cycle. A non-significant difference in the incidence of grade 3 or 4 neutropenia was found. This discrepancy may represent a non-specific immune response.

A possible explanation for the reduction in neutropenic fever events may be an anti-inflammatory effect which might be attributed to the presence of apigenin, a potent bioflavonoid found in WGJ (11) which inhibits the adhesion of leucocytes to endothelial cells (12). An anti-inflammatory effect of this extract was assumed also in a study concerning patients with distal ulcerative colitis who experienced a reduction in rectal bleeding following intake of WGJ (7).

In the current study, there was a less profound reduction in hemoglobin levels following the 3rd cycle of chemotherapy in the arm utilizing WGJ. Similarly, a reduction in the frequency of blood transfusions was found in a group of pediatric patients with thalassemia major following the intake of WGJ (8). Chlorophyll constitutes more than 70% of the solid content of WGJ. Believers of the alternative system of medicine claim that intake of WGJ enhances hemoglobin production due to the structural resemblance between the molecules of chlorophyll and hemoglobin (8). Although there is no data to support this hypothesis, one can speculate about the mechanism by which this effect is accomplished. Several enzymes involved in the mammalian haem biosynthesis are located in the mitochondria (13). Chemotherapy induces damage to the mitochondrial membrane (14). Chlorophyllin was found to be a protector of mitochondrial membranes against gamma-radiation and photosensitization (15) and may as well avoid the damage caused by some chemotherapy agents. This protection may restore the haem synthesis by maintaining activity of the mitochondrial enzymes involved in this process.

Myelosupression induced by the CAF regimen is caused mainly by doxorubicin and, to a lesser extent, by cyclophosphamide. One of the possible explanations for reducing myelotoxicity is that WGJ may change the metabolism of these drugs, resulting in a lower serum concentration of the active metabolites. If true, one would expect it to interfere with the antineoplastic effect as well. Such an unfavorable interaction was suggested with St. John's Wort which reduces the production of the active metabolite of irinotecan by the cytochrome P450 CYP3A4 enzymatic system (16,17). Although no such drug interaction was reported concerning the agents included in the CAF regimen (18), this possibility should be taken into consideration. A possible alternative mode of action of WGJ is by reducing the formation of reactive free radical intermediates which are induced by doxorubicin and can cause oxidative damage to cellular proteins as part of its cytotoxic effect (18). WGJ may block this oxidative stress by both the anti-oxidant vitamins, such as vitamins C and E, that it contains and by the large amount of chlorophyll that may act as an antioxidant scavenger. If true, this effect of WGJ may also diminish the antineoplastic effect of the CAF regimen. Although the most important

mechanism of antineoplastic action of doxorubicin is its interaction with topoisomerase II (18), the intake of the antioxidant vitamins in the WGJ is low (Table 2) compared to their amount in commercial pills of these vitamins, and the potential of compromising the desired cytotoxic effect of chemotherapy still exists. The dilemma concerning the concomitant administration of protective complementary agents along with chemotherapy is controversial. Antioxidant vitamins as normal cell protectors during chemotherapy were proposed by several authors (14,19,20), while others warn against using them on a regular basis due to a possible influence on the efficacy of chemotherapy (21).

In the current study, the reduction in the rate of chemotherapy-induced toxicity was not accompanied by any substantial compromise in the efficacy of chemotherapy against the tumor cells, as measured by the response rate in those patients with evaluable disease, by TTP in patients with stage IV disease, and by an early recurrence rate in non-metastatic patients. Nevertheless, the small number of patients in the study prevents any rigorous conclusions.

This study was designed in a prospective matched control format which enables dividing the population into two groups in which the main confounding variables are evenly distributed between groups without the need for a large number of patients. This design may be appropriate in a study such as the current one, which aims at achieving proof of concept. Selecting the pairs prospectively reduces the risk of selection bias. In any event, confirmation by a phase III study is needed before any recommendations can be made. Such a study should be based entirely on patients with stage IV disease so that the effect of WGJ on response to chemotherapy can be properly evaluated, along with its contribution to diminishing toxicity.

In the current study, frozen WGJ was used instead of a fresh extract, as was used in other studies (7,8). This was to avoid drop-outs due to difficulties in preparing fresh juice. In a test for amino acid levels, comparing fresh and frozen juices, a 20% reduction was found in the frozen juice (5). Vitamins levels were not tested but they are probably also reduced in the frozen extract. Actually, preparation of fresh juice is simple and this should be recommended in future studies.

The results were calculated as an intention-to-treat analysis, but 20% (6/30) of patients did not complete a full 9 wk of WGJ intake due to worsening nausea. Nausea was reported also in 33% of patients in the study of ulcerative colitis patients (7).

Nutrition support such as WGJ is very cheap, without any need for the involvement of the pharmaceutical industry. To the best of our knowledge, there are no nutrition recommendations regarding the prevention of chemotherapy-induced toxicity. The first step in this direction was taken in the current study. Confirmation by an appropriate phase III study may permit extraction of formal recommendations in the future.

Conclusion

WGJ taken during FAC chemotherapy may reduce myelotoxicity, dose reductions, and a need for GCSF support. These preliminary results need confirmation in a phase III study.

Acknowledgments and Notes

The authors extend thanks to Dr. Pnina Bar-Sella for sharing her knowledge with us and teaching us the right way to give WGJ, to Arka Stamper for growing the wheat grass and preparing the juice, and to Myrna Perlmutter for her help in the preparation of this paper. Address correspondence to Dr. G. Bar-Sela, Department of Oncology, Rambam Medical Center, POB 9602, Haifa 31096 Israel. E-mail: g_barsela@rambam.health.gov.il.

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