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# Original Research

## Evaluation of Wheat Grass in Preventing Haematological Toxicity Related to Chemotherapy in Breast Cancer Patients

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***ABSTRACT***

**Background:** Breast cancer is common in females and its treatment with chemotherapeutic agents is not free from hematological toxicity. There are many agents to ameliorate this toxicity. **Aim and Objective:** The present prospective, randomized, open label, comparative study was conducted in a tertiary care hospital to evaluate the effect of wheatgrass on hematological toxicity in breast cancer patients. **Material and Methods:** The standard anticancer therapy 5-Flourouracil (500mg/$m^2$), Adriamycin (50mg/$m^2$)/Epirubicin (100 mg/$m^2$), Cyclophosphamide (500mg/$m^2$) or Doxorubicin (60mg/$m^2$) and Cyclophosphamide (600mg/$m^2$) plus GCSF(300µgm). Group A served as control arm and Group B as test arm which received wheat grass two tablets (wheat grass ingredient 500 mg) three times a day beside the anticancer treatment. **Results:** The deterioration of hematological parameters (Haemoglobin, Platelet Count) produced in Ca breast patients by anti cancer therapy has been effectively prevented by the adding WG. Moreover, in the WG group there were less number of blood transfusions requirement compared to the control arm. **Conclusion:** The study concluded that wheat grass is effective in preventing the deterioration of hemoglobin and platelet count and curtailed the number of transfusions needed by patients of breast cancer on anticancer treatment.

**Key words:** Breast Cancer, Chemotherapy, Hematotoxicity, Wheat grass

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## INTRODUCTION

Breast cancer is a common disease in females (98%) and its prevalence is increasing with time. Although the incidence of breast cancer in India is lower than that in Western countries, but the mortality rates are disproportionately higher [1,2]. Besides radiotherapy and surgery, the pharmacological treatment involve two main modalities hormonal and non hormonal chemotherapeutic agents depending upon estrogen receptor status. However, these chemotherapeutic agents cause hematotoxicity and other adverse drug reactions (ADRs).

Most of the breast cancer patients present with deranged blood counts[3] and this is further compounded by hematological toxicity following use of the chemotherapeutics as they interfere with cell proliferation and differentiation in different blood lineages resulting in neutropenia, aplastic anaemia or thrombocytopenia [4]. Many other side effects observed with these drugs include cumulative dose related cardiotoxicity, mucositis, nausea and vomiting, reversible alopecia and local cutaneous reactions, etc [5].

The management of hematotoxicity is an essential component in the treatment of breast cancer and frequently require whole blood transfusions, vitamin B 12, granulocyte colony stimulating factor (GCSF), packed cells, iron and sometimes dose reduction of chemotherapeutic agents. However, even with above measures, the results are not always satisfactory and there is always a scope of research for finding out other alternatives. The herbal medications to improve blood profile with better outcome are some of the alternatives and one of them is wheat grass (WG) that has shown promising

results in thalasemia in decreasing number of blood transfusions requirement [6,7] WG has also shown positive results in chemotherapy induced hematotoxicity in various other cancers [8,9].

But there is paucity of research work in breast cancer, a single study in Europe has shown that WG cause reduction in myelotoxicity, need for GCSF support and decrease dose of chemotherapeutic agents [10]. Therefore, the current trial was conceived to evaluate the efficacy of wheat grass in preventing hematotoxicity produced by anticancer drugs.

## MATERIALS AND METHODS

A prospective, randomized, open label, comparative study was conducted in a tertiary care teaching hospital over a period of one year. Study was approved by Institutional Ethics Committee (IEC) Vide No.IEC/2016/313 dtd.4th November 2015 and registered with Clinical Trials Registry-India (CTRI). A written informed consent was obtained from the patients after fulfilling the inclusion and exclusion criteria.

An independent physician on duty available in AYUSH OPD running in the same hospital was consulted before allocating present herbal treatment in the study.

**Inclusion Criteria:** Newly diagnosed unilateral breast cancer, biopsy confirmed, Age between 40-70yrs, with or without co morbidities, without metastasis were included.

**Exclusion Criteria:** Bilateral breast cancer, moderate to severe hepato renal impairment, metastatic carcinoma, anaemia due to other reasons, other haematological disorders, patients with left ventricular ejection fraction<50% were excluded. No patient with fresh blood transfusion administered with in a week's time was enrolled in the study to avoid the fallacious or wrong interpretation of the effect of wheat grass.

**Treatment Protocol:**

Patients selected as per mentioned criteria were randomized using block permutation method into two groups (A and B). Both groups were given the standard anticancer therapy 5-Flouruouracil (500mg/$m^2$), Adriamycin (50mg/$m^2$)/Epirubicin (100 mg/$m^2$), Cyclophosphamide (500mg/$m^2$) or Doxorubicin (60mg/$m^2$) and Cyclophosphamide (600mg/$m^2$) plus GCSF(300µgm). Group A served as control arm and Group B test arm. In Group B wheat grass two tablets (wheat grass ingredient 500 mg) three times a day were added. Dose of wheat grass used in current study was based on the dose used by Jigisha MS *et al*, 2015 [9].

The basic supportive treatment in form of multivitamins (vitamin B12 and folic acid) and iron supplements of same composition and strength were allowed in both treatment arms. Erythropoietin was not allowed to any patient during the study and blood transfusion requirement was based on the guidelines of GRADE system used by Szczepiorkowski Z M *et al* 2013 [11] , in their study where patients with Hb<7g/dl were given blood transfusion. Before administering the regimen in both groups the baseline parameters (pre-drug score or 0) was evaluated. Patients were followed up on 3, 6 and 9 weeks. All parameters of blood were checked (hemoglobin , total leucocytes count, platelets). Besides this, any adverse drug reaction (ADR) during study was also recorded. Patients drop out, number of blood transfusions required and dose reduction if any was also noted.

## RESULTS

A total of sixty breast cancer patient aged between 40-70 yrs were included in the study. All the patients completed the study and majority of patients were from rural area, non smokers, postmenopausal with positive hormonal status. **(Table 1)** In group A there was significant decrease in Hemoglobin, platelets, while in group B there was significant increase in hemoglobin, platelets. Total Leukocyte Count did not show any change in either group. On intergroup comparison the increase in haemoglobin in Group B showed significant increase in hemoglobin levels (p=0.009, p=0.0008, p<0.0001 at 3,6,9 weeks respectively) and platelets in group B at six weeks (P<0.0163) when compared with Group A.

Although statistically significant these results may not be clinically significant except that wheat grass has largely prevented the deterioration of haemoglobin and platelets in Group B. **(Table 2)** On intergroup comparison it was found that group B had significant increase in hematological parameters like hemoglobin, platelet counts then group A. Number of blood transfusions required due to fall in hemoglobin were given compared and a total of twenty three Blood transfusions were required in Group , while in Group B only three blood transfusions were needed. **(Table 3)**

**Table No.1: Basic Demographic Parameters of the patients in both the groups n=60)**

| Parameter | Group A (n=30) | Group B (n=30) |
|---|---|---|
| Mean Age | 48.07±11.017( in yrs) | 51.13±12.057( in yrs) |
| Residence | Urban 30% : Rural 70% | Urban 20% : Rural 80% |
| Smoker Vs Non Smoker | 5vs 25( 16.7% : 83.3%) | 8 vs 22(26.7% : 73.3%) |
| Post Vs Peri Menstrual | 15 vs 15 (50% : 50%) | 17 vs 13 (56.7% : 43.3%) |
| Family History Vs Negative Family History | 14 vs 16 (46.7% : 53.3%) | 9 vs 21 (30% : 70%) |
| Hormonal Status | Positive 25 vs Negative 5 (83.3% : 16.7%) | Positive 22 vs Negative 8 (73.3% : 26.7%) |

**Table 2: Effect of anticancer drugs alone( group A) and with their combination with WG ( group B) and Intergroup Comparison on Hematological Parameters**

**(n=60)**

| **Parameter** | **HAEMOGLOBIN (Mean±SEM) (gm%)** | | | |
|---|---|---|---|---|
| **Weeks** | **Baseline** | **3 Weeks** | **6 Weeks** | **9 Weeks** |
| **Group A n=30** | **10.04±0.195** | **8.72±0.245** p<0.0001**** | **8.82±0.259** p=0.0002*** | **8.53±0.231** p<0.0001**** |
| **GroupB n =30** | **9.79±0.176** | **9.65±0.240** p=0.3875 NS | **9.96±0.189** P=0.1511 NS | **10.28±0.219** p=0.0068** |
| **P value** | **=0.3519NS** | **=0.009**** | **=0.0008***** | **<0.0001**** |
| **Parameter** | **TOTAL LEUCOCYTE COUNT (Mean±SEM) (th/mm3)** | | | |
| **Weeks** | **Baseline** | **3 Weeks** | **6 Weeks** | **9 Weeks** |
| **Group A** | **8030±315.29** | **8110±281.84** p=0.8147NS | **7926.33±272.21** p=0.7958 NS | **7786.67±300.83** p=0.6284 NS |
| **Group B** | **7808±347.99** | **7837.67±345.67** p=0.9256 NS | **7580±303.22** p=0.4582 NS | **7673.33±274.09** p=0.7368 NS |
| **P value** | **=0.6382NS** | **=0.5438 NS** | **=0.3989 NS** | **=0.7816 NS** |
| **Parameter** | **PLATELETS (Mean±SEM) (th/mm3)** | | | |
| **Weeks** | **Baseline** | **3 Weeks** | **6 Weeks** | **9 Weeks** |
| **Group A** | **2.37±0.120** | **2.27±0.1099** p=0.329 NS | **1.92±0.088** p=0.0002*** | **1.99±0.095** p=0.0195* |
| **Group B** | **2.15±0.105** | **2.31±0.1171** p=0.0057*** | **2.23±0.091** p=0.4670 NS | **2.46±0.087** p=0.0087*** |
| **p value** | **=0.1825NS** | **=0.8347 NS** | **=0.0163*** | **=0.0007***** |

The data is shown in Mean SEM. Paired Student 't' test in comparison to respective baselines. * P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001, NS-Non Significant. Comparison between two groups at 3, 6 and 9 weeks with Unpaired Student 't' test was statistically significant for haemoglobin, Non significant for TLC and significant at 6 and 9 weeks for platelets.

**Table 3: Blood Transfusion Requirement in Both the Groups (n=60)**

| **Weeks** | **Group A(n=30)** | **Group B(n=30)** |
|---|---|---|
| **Baseline** | 0 | 0 |
| **3 Weeks** | 8(34.78%) | 3(100%) |
| **6 Weeks** | 8(34.78%) | 0 |
| **9 Weeks** | 7(30.43%) | 0 |
| **Total** | 23(76.66%) | 3(10%) |

## DISCUSSION

Wheat grass a herbal preparation has shown encouraging response to boost haemopoetic parameters in Thalasemia [6,7,12] and has also been tried in carcinoma [13, 14]. There are couple of reports that wheat grass may improve hematological toxicities related to the breast cancer [10, 14].

The results of the present trial revealed that hematological parameters in group B showed improvement in Hb, platelets. These findings are consistent with number of studies showing deterioration in hematological parameters due to myelosuppression with anticancer drugs [4,10,15,16].

Bar Sela-G *et al*, 2007 [10] has found that WG during FAC chemotherapy in breast carcinoma resulted in reduction in myelotoxicity, dose reduction and need for GCSF or erythropoietin support (p=0.01). These results are in concurrence to our results demonstrating WG's positive potential in reducing myelotoxicity.

Thrombocytopenia is common in carcinoma patients because of chemotherapy, radiation or from underlying disease itself, [17,18] Alkylating agents and cyclophosphomide affects stem cell, megakaryocyte progenitors, prevents release of platelets from megakaryocytes and promotes platelets apoptosis [19].

Trigar P R *et al*, 2011 and Khan N *et al*, 2015 [8, 20] have found similar results to current study in animal models as WG improved hematological parameters (RBC, TLC, DLC and Platelet count)

WG has shown promising results in carcinoma and hematological disorders because of its anti-inflammatory, antioxidant (vitamins C & E and selenium), bioflavonoid, minerals and anti aging properties [9,21,22,23,24].

Antioxidant activity of WG prevent oxidative damage to DNA, Lipid peroxidation, stimulation of gap junction communication, effect on cell transformation and differentiation, inhibition of cell proliferation and oncogene expression, effects on immune functions and inhibition of endogenous formation of carcinogens [25].

Another constituent of wheat grass implicated in an anticancer activity is hormone Abscisic Acid (plant hormone ABA) which can neutralize the effect of human chorionic gonadotropin and a compound similar to this hormone has been found to be produced by cancer cells. Wheat grass has also been shown to inhibit human cancer cells proliferation via cell cycle G1 arrest and P53 induction and also down regulation of cyclin D1/CDK4 binding thereby inhibiting cell proliferation [26].

The WG has up to 70% of chlorophyll (known as green blood) a blood builder as both chlorophyll and human hemoglobin (Hb) share an identical atomic structure in having tetra pyrrole rings with only major difference that magnesium in central metal atom in chlorophyll instead of iron as in hemoglobin. Magnesium is beneficial for about 30 enzymes. Chlorophyll also contains superoxide dismutase that decomposes superoxide radicals in the body[27].

Chiu *et al*, 2005 [28] has shown that the chlorophyll retard human breast carcinoma cell (MCF 7 cell) and deactivates ERKS (Extracellular Signal Regulatory Kinases) belonging to subfamily of MAPKS to inhibit the breast cancer cells proliferation.

Combinations of FAC/FEC/DC used in carcinoma breast are known to cause myelosuppression, immunosuppressant, GIT stress, anemia, neutropenia, hepatotoxicity, asthenia/fatigue, stomatitis, myalgias, dysguesia, alopecia on short term basis [29]. While on long term these drugs may cause cardio toxicity, secondary leukemia, decline in cognitive function, neurotoxicity, adverse effects on fertility, premature menopause, teratogenicity and thrombophlebitis [30].

WG has been shown to reduce myelotoxicity, dose and need for GCSF without diminution of the efficacy of chemotherapy [10]. Clinical trials show that WG induce synergistic benefits to chemotherapy and attenuate chemotherapy related side effects. [31] Even earlier work on mice has also demonstrated that WG did not produce any significant side effects [32] In leukemia patients WG when added significantly reduced the severity of nausea, vomiting, bone pain, fever, skin rash, hair loss, mouth ulceration, anorexia and loss of weight and in addition improved hemoglobin, red blood cell count and platelet [9].

WG group required only three transfusions while patients in group A needed 23 transfusions. This finding is important in view of hematotoxicity by these anticancer drugs. Review of literature failed to show any report on the effect of WG on transfusion requirement in breast cancer patients. However, WG beneficial effects thalasemia has been recorded by increase in hemoglobin , and decrease in the requirement of packed red cells, blood transfusion requirements. [6,7,12,33] However, there were few limitations of current trial as it was an open label, short duration study of nine weeks only, covering three cycles of chemotherapy. No attempt was made to study the dose response. What will effect on long term basis needs further investigation.

## CONCLUSION

The deterioration of hematological parameters (Haemoglobin, Platelet Count) produced in Ca breast patients by anti cancer therapy has been effectively prevented by the adding WG. Moreover, in the WG group there were less number of blood transfusions requirement. Since it was an objective method, nothing can be commented upon the ADRs in both the groups. The results of the present preliminary study thus are encouraging but require larger adequately powered clinical trials in future to substantiate these findings before it can be recommended in general.

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