Original Article-II

An Ayurvedic Herbal Compound to reduce Toxicity to Cancer chemotherapy: A Randomized Controlled Trial.

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ABSTRACT

Background: Maharishi Amrit Kalash (MAK) is an ayurvedic compound containing many herbs rich in antioxidants. We evaluated its role in reduction of chemotherapy toxicity among women with breast cancer.

<u>Patient and Methods:</u> We recruited 214 patients with breast carcinoma receiving cyclophosphamide, methotrexate and 5-flourouracil (CMF) or cyclophosphamide, adriamycine, & 5-flourouracil (CAF), adjuvant or neo-adjuvant chemotherapy. The toxicity of chemotherapy was assessed according to WHO criteria. Statistical analysis was carried out on Epi-info 6 and STATA-7. All patients received same anti-emetic therapy with ondensetron and dexamethasone.

Results

There was a significant reduction in toxicities observed in MAK group throughout chemotherapy cycles: Poor performance status was prevented by concomitant administration of MAK along with chemotherapy.(Prevented Fraction (PF)=60.6% (95% confidence interval 22.1 to 80.1 ; p value =0.005). Vomiting was prevented by MAK {PF=40.3%, (95% confidence interval 15.1 to 58.1; p value=0.002)}. Similarly anorexia was reduced with PF= 35.6%. (95% confidence interval 17.6 to 49.7, p value = 0.0001) in MAK group. No improvement occurred in stomatitis, diarrhea, alopecia and leucopenia. No overgrowth of tumours occurred in the group treated with Neoadjuvant chemotherapy receiving MAK.

Conclusion:

MAK may be used as a supplement along with chemotherapeutic drugs for reducing chemotherapy induced vomiting, anorexia and improving general well being of patients.

INTRODUCTION

Incidence of breast carcinoma has increased exponentially in the last decade. Surgery is most effective local therapy with chemotherapy and radiotherapy used as an adjunct. Chemotherapy is associated with significant side effects and toxicities, resulting in high dropout rates and morbidity. Many drugs like mesna with Ifosfamide have been tried to prevent or control chemotherapy related toxicities, but these agents have their own side effects.[1] Other cytoprotecter like Amifostine have also showed side effects like transient hypotension ,dizziness and hypocalcaemia.[2] There is a need to explore an ideal chemo-protective agent without toxic effects.

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The modern healthcare provider is exploring the beneficial effects of many herbs and natural products in treating and preventing many disease states. Maharishi Amrit Kalash (MAK), MAK-4 and MAK-5 collectively is an herbal formulation derived from the Indian system of medicine known as '*Ayurveda*'. This herbal formulation has been used for general betterment of health since antiquity. The MAK-4 is prepared in a paste form while MAK-5 is dispensed as tablets. The ingredients of MAK-4 are *Terminalia chebula, Phyllanthus emblica, Elettaria cardamomum, Cyperus rotundus, Curcuma longa, Piper longum, Santalum album, Cyperus scariosus, Mesua ferrea, Convolvulus pluricaulis, Glycyrrhiza glabra, Embelia ribes, Centella asiatica*, ghee, honey and sugar. The ingredients of MAK-5 are *Withania somnifera, Glycyrrhiza glabra, Ipomoea digitata, Asparagus adescendens, Emblica officinalis, Tinospora cordifolia, Asparagus racemosus, Convolvulus pluricaulis, Vitex trifolia, Argyreia speciosa, Curculigo orchioides, Capparis aphylla, Acacia arabica*.

MAK seems to have a potential to reduce the chemo-toxicity,[3,4] as well as tumouricidal activities in animals.[5,6] MAK has also been shown to reduce metastasis in animal models[7] Antioxidant properties of MAK have been reported by many experimental and clinical studies.[3,8,9,10,11] Misra et al (1994) conducted initial prospective study in 62 patients receiving a variety of combination Chemotherapy (in one of the combinations of cyclophosphamide, methotrexate, vincristine, doxorubicin, cisplatin, prednisolone and 5-FU) for various types of tumours including non-Hodgkin's lymphoma, ovarian cancer, breast cancer, oral cancer and osteogenic sarcoma. They demonstrated a reduction in severity of vomiting and diarrhoea and improvement in sleep and general well being. This study was nonrandomized with a small sample size. Patients were suffering from different types of cancers receiving different chemotherapy regimen and chemotherapy toxicity was not assessed as per WHO criteria. Thus, usefulness and significance of this study was limited.[3] In another study, we observed protective effect of MAK in vomiting, diarrhea and maintenance of general well being of

patients with breast carcinoma in 129 cases.[4] The present paper describes the detailed results of a randomized trial carried out on a larger sample size to assess the effectiveness of MAK in reducing the chemotherapy related side effects.

Material and Methods:

A total of 214 breast cancer patients, receiving chemotherapy were included in the study from Breast Cancer Clinic, Department of Surgery, All India Institute of Medical Sciences, New Delhi. The study was commenced in May 1997 and ended in January 2003. We hypothesised that the administration of MAK herbal compound can reduce the toxicity of anticancer chemotherapy in women with breast cancer. The sample size was calculated as follows. The prevalence of nausea and vomiting after combination chemotherapy (CMF) is about 0.9 for a 20% reduction in the prevalence with a confidence levels of 95% $(1-\alpha)$ and power of 80% $(1-\beta)$. We needed to study 142 subjects (71 in treatment arm and 71 in control arm). During the course of the study it transpired that many patients were dropping after only 2 to 3 cycles of chemotherapy. Hence we recruited more number of patients to obtain the desired statistical power.

The project was formally approved by hospital Ethics committee. Patients with breast cancer receiving chemotherapy were included in the study. The diagnosis of breast cancer was confirmed histologically. Patients suffering from diabetes mellitus were excluded from study, as MAK-4 is a sugar based compound.

Patients with early stage of breast cancer were offered initial surgery followed by six cycles of CMF, as adjuvant chemotherapy at 21 days interval.

Patients with inoperable or locally advanced carcinomas were given 3 cycles of CAF as neo-adjuvant chemotherapy followed by surgery provided there was complete or partial response to the therapy and then remaining 3 cycles were given as completion chemotherapy. In general the CMF regimen was employed as a postoperative adjuvant, following mastectomy or wide excision along with full axillary dissection in T1, T2- N0 or N1 disease. The CAF regimen was used as neo-adjuvant therapy in women with locally advanced breast cancer (LABC).

Women were randomized to receive MAK supplement along with chemotherapy while the other half served as control and given CMF or CAF alone. Patients were monitored for toxicity.

Method of Randomization: We used simple randomization method with an allocation ratio of 1:1. The randomization schedule was generated from a table of random numbers. The patients were given written information about the nature of trial and requested to sign a consent form. The patients were randomized into two groups- MAK and control group by two Ayurvedic physicians, using sealed numbered envelopes. Patients in MAK group received MAK–4 paste with dosage of 2 tablespoonfuls twice daily with a glass of milk and MAK-5, 2 tablets twice daily with lukewarm water half an hour after MAK-4. This MAK supplementation was given throughout the chemotherapy i.e. for approximately 18 weeks and responses were evaluated by questionnaire and direct physical examination at 21 days interval.

Tumour regression was measured according to EORTC response criteria.[12]

Statistical analysis: Analysis was carried out on Epi-info 6 (WHO Geneva,Switzerland) and STATA-7 (Stata Statistical package, Texas, USA). A risk or cumulative incidence (CI) of each side effect of chemotherapy has been calculated by using the following formula:

CI = Number of cases with toxicity/Total number of cases in that group.

The relative risk (RR) was computed as CI of MAK/ CI of Control. The point estimates and 95 % confidence interval of RR have been calculated with Epi- info 6(WHO) .The effect of MAK in preventing the toxicity is expressed as prevented fraction (PF) [PF= incidence in unexposed - incidence in exposed)/ incidence in unexposed].

The statistical significance was calculated by applying Fisher's exact test with 2-tailed p values.

TABLE:1

VARIABLES (mean{SD})	MAK (n=102)	CONTROL(n=112)
AGE (Years)	44(10)	44.9(8.9)
WEIGHT (KG)	57.1(11.6)	59(13.1)
Mean WBC (x10^9/L)	7474(2445)	7877(2227)

The patients in control group received chemotherapy and other supportive care only. No placebo has been administered to patients of control group. Both groups of patients received Ondansetron intravenously with each dose of chemotherapy and then orally for 2-3 days. Dexamethasone was also injected just prior to chemotherapy in a dosage of 8mg intramuscular and 8 mg intravenous. Pain killers and antibiotics for infections has been used as concomitant therapy for infections during study. Compliance was checked by our research fellows by checking the bottle of tablets (MAK5) from time to time and counting the number of tablets.

The MAK was manufactured and supplied by sponsor after assuring the good quality control and standardization (with minimal variation from batch to batch).

Results and Analysis:

Out of 214 patients, 102 patients were recruited in MAK group and 112 patients in the control group. We have included 181 (85 in MAK & 96 in control) patients (those completing at least three cycles of chemotherapy) in final analysis of data (please see flow chart). The data of remaining 33 patients were not evaluated due to following reasons.

(1) Lost to follow up during study.

(2) Due to progressive disease chemotherapy was stopped in some patients.

(3) Some patients refused further treatment and went away.

One hundred twenty one patients received adjuvant chemotherapy (56 in MAK & 65 in control) and 93 patients received neo-adjuvant

chemotherapy (46 in MAK & 47 in control). One hundred and nine patients received CAF (51 in MAK & 58 in control) and 105 patients received
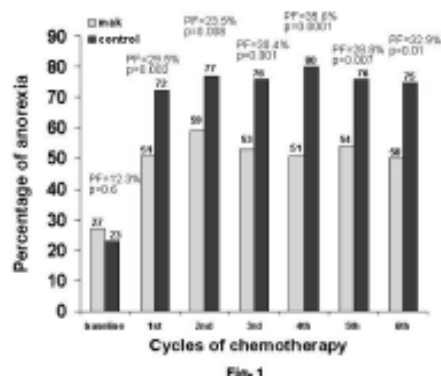

Fig 1: Depicting Cumulative Incidence of Anorexia in the MAK and Control Groups in Different Cycles of Chemotherapy

CMF (51 in MAK & 54 in control). In MAK group age range was 23 to 79 years with mean age of 44.3 years and in controls, it ranged from 23 to 72 years with a mean of 44.7 years.

There was no significant difference in baseline parameters in both groups. A reduction of chemotherapeutic toxicity was observed in the following side effects:

Anorexia:

Throughout chemotherapy patients receiving MAK had better appetite when compared to controls (Figure 1). Appetite was coded in three categories. The patients with fair and poor categories were grouped together for analysis.

Statistically significant differences were observed in all the cycles. At 4th cycle of chemotherapy 51.35% patients in MAK experienced fair & poor appetite as compared to 79.76 % patients in control arm (RR = 0.64; 95% confidence interval 0.50 to 0.82; p < 0.001). The PF was 35.6%. (95% confidence interval 17.6 to 49.7)

Vomiting:

We categorized the data into two groups i.e. vomiting present or absent. (Figure-2) MAK reduced the risk of vomiting with statistically significant difference in 3rd cycle of chemotherapy (p =0.002, RR 0.60; 95% confidence interval 0.42 to 0.85) PF=40.3, (95%
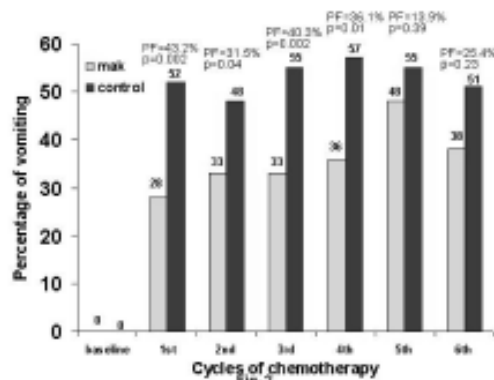

Fig 2: Depicting Cumulative Incidence of vomiting in the MAK and Control Groups in Different Cycles of Chemotherapy

confidence interval 15.1 to 58.1) and for 4th cycle of chemotherapy (p=0.01, RR 0.64; 95% confidence interval 0.45 to 0.91) PF=36.1, (95% confidence interval 9.1 to 55.1). The differences in other cycles was not statistically significant.

Karnofsky Performance Status:

KPS score assessed the overall state of health and physical performance. Patients were categorized in two groups i.e. KPS ≤70% or ≥80% Patients with deteoriating condition (KPS ≤70% were more in controls as compared to MAK group.

As shown in (Figure 3) At the end of 3rd cycle patients with poor status were more in controls as compared to MAK group (p=0.01 RR= 0.51; 95% confidence interval 0.30 to 0.88) PF=48.7 (95% confidence interval 12.3 to 70). As chemotherapy progressed at the end of 5th cycle, highly significant statistical difference was observed. (p=0.005, RR 0.39; 95% confidence interval 0.20 to 0.78) PF=60.6 (95% confidence interval 22.1 to 80.1).

Weight:

Among women receiving neoadjuvant therapy with CAF the body weight was maintained in MAK group, mean difference in body weight (pre chemotherapy weight - post chemotherapy weight) was 0.81 kg (p=0.26, t=1.13) whereas women in control group experienced mean weight loss of 1.58 kg, which on paired t test was statistically significant (p= 0.01, t= 2.33).

In case of CMF group there was an average increase in mean body weight in both group but the weight gain was more pronounced in the MAK

group (1.68kgs; 95% CI 2.9 to 0.37, t=2.59, p=0.01) compared to control group (1.28kgs; 95% CI 2.54 to 0.026, t=2.05,p=0.04)

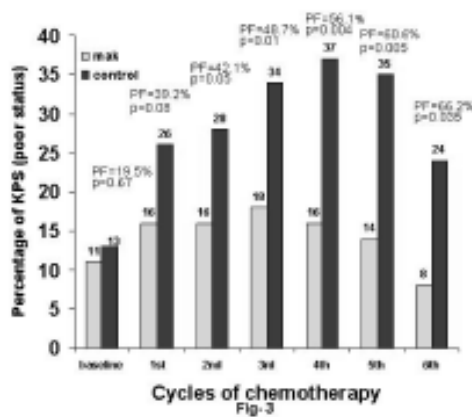Thus, intake of MAK helped in maintenance of body weight in through out the chemotherapy

Fig 3: Depicting Cumulative Incidence of Karnofsky performance Status in the MAK and Control Groups in Different Cycles of Chemotherapy

Stomatitis:

Stomatitis was recorded in 4 categories. The patients in 2, 3 & 4 categories were grouped together for analysis. At the end of 4th cycle, cumulative incidence of stomatitis was less in the MAK group (14) as compared to controls (23) (PF=40.3%, p=0.15) but there was no statistically significant difference observed in any cycle (Figure 4).

Other side effects:

Diarrhoea:

The incidence of diarrhoea was similar in both groups at baseline (table 1). After 3 cycles 76.5% patients had no diarrhea, 16.5% had >2 days and 7.1% had diarrhoea >2 days. Similarly at the end of 3rd cycle in control group 13.4% patients reported diarrhoea <2 days, 7.2% reported >2 days and 1% patients required therapy to control diarrhoea.

After completion of 6 cycles in MAK group 10.2% had diarrhoea <2 days, 2% had >2 days and in control group 12.5% had diarrhoea <2 days and 7.1% reported diarrhoea >2 days.

Although in last two cycles less diarrhoea were observed in MAK group but the difference was not statistically significant (p=0.6) (Figure 5).
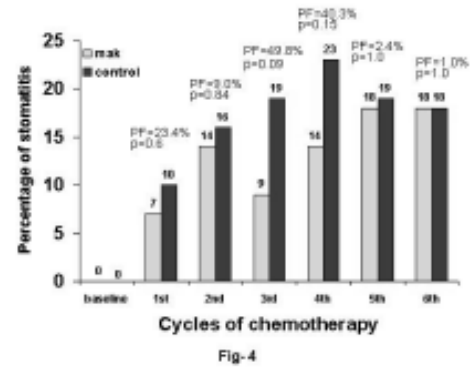

Fig 4: Depicting Cumulative Incidence of stomatitis in the MAK and Control Groups in Different Cycles of Chemotherapy

Leucopenia:

At baseline no difference was observed in both groups *(Table 1).*Mean total leukocyte counts (TLC) 6026(2085) and 6080(2424) were observed in MAK and control groups respectively at the end of 3rd cycles. After completion of chemotherapy mean TLC 5407(1681) and 5707 (2155) were observed in MAK and control groups.

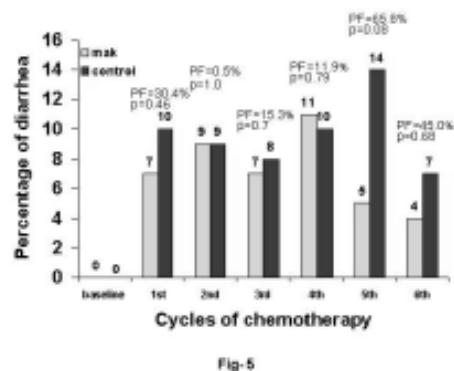In case of leucopoenia (total leucocytes count< 4000), no significant difference was observed between two groups.

Fig 5: Depicting Cumulative Incidence of diarrhea in the MAK and Control Groups in Different Cycles of Chemotherapy

Alopecia:

At the end of chemotherapy 38.8% and 32.1% patients from MAK and control groups reported minimal alopecia. Moderate alopecia were observed 28.6%, which was similar in both groups. Complete alopecia was observed in 20.4% and 26.8% in MAK and control group respectively, p=ns.

Tumour Response:

Tumour response was measured in patients receiving neo-adjuvant chemotherapy for locally advanced disease. In MAK group, out of 39, ten patients had complete response (CR) and sixteen patients had partial response (PR). Similarly in case of controls, out of 43 patients, ten had CR and 19 patients had PR. Six cases MAK and 4 cases in the control arm developed progressive disease.

DISCUSSION

In this study we tried to evaluate the effect of MAK as a chemo protective agent in patients with breast cancer. The most common side effects associated with CAF and CMF are anorexia, vomiting, Stomatitis, diarrhoea, alopecia, decrease performance status and leucopoenia. In our study, there was significant amelioration in certain side effects. Patients receiving MAK had shown significantly better improvement in appetite as compared to controls, throughout chemotherapy.

5- hydroxytyptamine ($5HT_3$) receptor antagonist e.g. Ondesteron have been used to prevent nausea and vomiting, but have their own side effects. The present study points out that MAK reduces the risk of vomiting as compared with controls significantly in initial cycles of chemotherapy.

KPS is a measure of the physical activity status of patients. Patients with KPS $\geq 70\%$ score indicate near normal activity. As chemotherapy progresses the KPS of patients often deteriorates. KPS of less than 70% indicate that patients are not able to fend for themselves. A score of less than 5 indicates the need of considerable assistance and frequent medical care.

Patients with KPS $\leq 70\%$ were more in control than in MAK group. At the end of chemotherapy, 8% of patients in the MAK group had a KPS of $\leq 70\%$ compared to 23.6% in the control group. This indicates that MAK is helpful in enhancing the general performance status of patients.

Misra et al reported reduction in frequency of vomiting, diarrhea and improvement in general well being of patients taking MAK.[3] They observed a reduced risk of diarrhoea and stomatitis. Women in CMF group gained weight more so in the MAK group. Among women receiving CAF there was a net loss of body weight of 1.5kg in the control group. MAK administration in the CAF group helped in maintaining their body weight.

No difference was observed in between groups as regards alopecia, and leucopenia.

Various hypothesis have been put forward to describe the mechanism of action of MAK. MAK has been found to have antioxidant and free radical scavenging properties in animals.[9] Free radicals and relative oxygen species have been shown to be related with the pathogenesis of cancer and other degenerative diseases. Ionizing radiation and chemotherapeutic agents also produce excess of free radicals, which eventually lead to damage of the tissues. Super oxide dismutase (SOD) is a naturally occurring enzyme in human cells, which buffers free radicals by dismutation. This enzyme is not adequate in presence of excess of free radicals.

MAK contains low molecular weight antioxidants. Niwa et al (1989) have demonstrated that lipid peroxide; free radical falls from abnormal to normal levels by supplementation of MAK. It has also been shown that MAK potentiated SOD enzyme induction capacity of human leukocytes.[10] MAK also inhibits the free radical mediated peroxidation of microsomal lipids in vitro.[11] Significant reduction in lipid peroxide was also observed by

TABLE:2

VARIABLES (WHO Grading)*	MAK (n=102)	CONTROL (n=112)
ANOREXIA		
(1)	73.8%	76.7%
(2)	24.3%	22.4%
(3)	1.9%	0.9%
VOMITING		
(0)	96.3%	92.2%
(1)	3.7%	6.9%
(2)	0	0.9%
KPS		
(8)	13.1%	9.5%
(9)	24.3%	26.7%
(10)	52.3%	50.9%
DIARRHEA		
(0)	98.1%	99.1%
(1)	1.9%	0.9%
STOMATITIS		
(0)	96.3%	97.4%
(1)	3.7%	2.6%
ALOPECIA		
(0)	99.1%	99.1%
(1)	0.9%	0.9%

MAK in human beings.[3]

Limitations of this study is that the study design was open randomized because there was a difficulty to make similar placebo like paste.

In summary MAK seems to have a potential as chemoproective agent. We are planning to study this compound in double blind placebo controlled trial to confirm these findings.

ACKNOWLEDGEMENTS:

REFERENCES:

1.   Dechant KL, Brogden RN, Pilkington T, Faulds D ifosfamide/mesna. A review of its antineoplastic activity, pharmacokinetic properties and therapeutic efficacy in cancer. Drugs. 1991;42(3):428-67.

2.   Genvresse I, Lange C, Schanz J, et al. Tolerability of the cytoprotective agent in amifostine in elderly patients receiving chemotherapy: a comparative study. Anticancer Drugs; 2001;:12(4):345-9.

3.   Misra N.C. Sharma H.M, Chaturvedi A, et al., Antioxidant adjuvant therapy using natural herbal mixtures) MAK-4 and MAk-5) during intensive chemotherapy reduction in toxicity. A prospective study of 62 patients. Proceeding of the XVI international cancer congress Bologna, Italy, Monduzzi editore, 1994;3099-3102.

4.   Samaiya A, Srivastava A, Tarnakanti V, et al.,

Reduction on toxicity of cancer chemotherapy by maharishi amrit kalash (MAK)-An ayurvedic herbal compound. Annal National Academic medicine science (India) 1999;35(2):109-119.

5.   Sharma HM, Dwivedi C, Satter BC, et al., Antineoplastic properties of Mahrishi-4 [MAK-4] against DBA- induced mammary tumours in rats. Pharmacology, Biochemistry and behavior, 1990;35:767-773.

6.   Sharma HM, Dwivedi C, Satter BC, Abou-Issa H. Antineoplastic properties of Maharshi Amrit Kalash [MAK-5], An ayurvedic food supplement, against 7,12-Dimethylbenz (a) anthracene-induced mammary tumours in rats. Journal of Research and Education in Indian Medicine, 1991;10(3):1-8.

7.   Patel VK, Wang J, Shen RN, Sharma HM, Brahmi Z. Reduction of metastases of Lewis lung carcinoma by an ayurvedic food supplement [MAK-4] in mice. Nutrition research, 1992;12:51-61.

8.   Bondy. SC, Hernadez. T.M, Matia. C. Antioxidant properties of two ayurvedic herbal preparations [MAK-4and MAK-5]. Biochemical Archives, 1994;10:25-31.

9.   Niwa .Y. Effect of Maharshi-4 [MAK-4] and Maharshi-5 [MAK-5] on inflammatory mediators- with special reference to their free radical scavenging effect. Indian journal of clinical practice, 1991;8(1):23-27.

10.   Niwa. Y.The importance of superoxide dismutase functioning and marked anti-oxidant activity demonstrated in Maharshi Amrit Kalash.International Symposium Ultrecht,The Netherlands 9 sept 1989 (Abstract).

11.   Dwivedi C, Sharma HM, Dobrowski S, Engineer N. F. Inhibitory effects of Maharshi-4 [MAK-4] and Maharshi-5 [MAK-5] on microsomal lipid peroxidation. Pharmacology, Biochemistry and Behavior, 1991;39(3)649-652.

12.   Tumour eligibility and response criteria for phase ï & ø studies. Brussels: EORTC Data Center Manual 1992.