DISCUSSION

A) Discussion on need of management of chemotherapy side-effects with Ayurvedic medicines

Management of chemotherapy induced side effects described above is a perpetual problem in giving chemotherapy in breast cancers. The allopathic modalities of management of side effects are rather peripheral, which include nutritional support to minimize the weakness, pain control to reduce the sufferings, control of bleeding to counteract the blood loss by administering the blood clotting factors, correcting the blood loss by blood transfusion, iron supplements, intake of heamatinic. Allopathic management of side effects includes anti emetics, antihistaminic, antacids, purgatives, antidiarrhoeal, antibiotics, steroids, injections of filgrastin to increase the leucocytes counts and to counteract the myelosupression caused due to chemotherapy. Still with this management the cancer patients suffer from the severe clinical manifestation of the symptoms like anorexia, nausea, vomiting, taste abnormality, constipation, diarrhea, alopecia skin and nail discoloration, hyperpigmentaton and severe myelosupression. The general condition of patients worsens due to these side-effects. The quality of life is not well maintained during the course of chemotherapy. Due to this fact most of the patients are not in condition to tolerate chemotherapy or to complete the recommended cycle of chemotherapy in expected time limit. In this scenario, Ayurvedic medicines could help to minimize the side effects, enhance the immunity, and increase the strength physically as well as mentally. Patients could complete chemotherapy protocols in the due course of time. In this respect, the study conducted and data presented here is very useful. The Ayurvedic drugs used are non-toxic, easily palatable and not very expensive, and the effect appears to be very significant. The study was carried out in 2 groups. Group A was study group of 50 patients who had received Ayurvedic treatment (CG4 – combination of four Ayurvedic medicine ie Mautikyukta Kamdudha, Maukticyukta Pravalpanchamrut, Pandmakadi ghruta, Shatavari Kalpa) during chemotherapy and thereafter. Group B was the control group of 50 patients who had received chemotherapy as described earlier.
B) Discussion on Demographic data

Patients diagnosed with breast cancer and underwent chemotherapy are mostly in between the age group of 31 to 70 yrs. in both the groups. This group comprises of perimenopausal and menopausal stage in which the hormonal changes occur frequently. 40% patients were in the 50 years onwards age group. This age is considered as older & it seems that the occurrence of cancer progresses as per the age. 53% patients are from hormonally active age group. 80% patients of breast cancer underwent chemotherapy after surgery. It is because; the chemotherapy is the most recommended conventional treatment available for breast cancer after surgery. 97% patients were diagnosed as infiltrating ductal carcinoma. This type of breast cancer shows maximum prevalence in this study. Infiltrating ductal cancer or Invasive ductal cancer is the most common type of breast cancer. In stage wise distribution of breast cancer 50% patients are of stage III and 30% patients are of stage II. 80% of the patients were receiving chemotherapy after surgery that is adjuvant chemotherapy. 76% patients were from middle socio economic group. In occupation-wise distribution 65% patients were the housewives. In 65% of patients no any specific type of addiction was found. In this study patients who underwent chemotherapy before surgery are less than those who underwent chemotherapy after surgery which is dependent upon the decisive factors namely the stage of the disease and age of the patient.

C) Discussion on mode of action of combination of Ayurvedic medicines on side-effects of chemotherapy –

Side-effects exhibited by chemotherapy drugs like vomiting, loss of appetite, nausea, diarrhea, constipation, GI bleeding, stomatitis, weakness, skin rash are mainly seen by dushti of Vata and Pitta dosha. These drugs have direct effect on Rasa, Rakta, Asthi, Majja and Shukra dhatus. Chemo drugs also vitiate Rasavaha, Raktavaha, Annavaha Strotas. The Jatharagnidushti and Ojakshaya are also caused due to the toxic effects of chemotherapy drugs. Pitta dushti causes Rakta dushti, as Rakta and Pitta being interdependent. Toxins produced are circulating with Rakta dhatu throughout the body causing the systemic side effects. The side effects of chemotherapy thus produced are systemic as well as generalized like Chhardi (vomiting), Raktapitta
(bleeding through openings of the body), Sarvanga Daha (burning in the body), Twakdushti (skin pigmentation), Malavashtambha (constipation), Khalitya (alopecia), Khushdhgamandya, Anannabhilasha (anorexia), Dourbalya (weakness) etc.

Patients from Group A received combination of oral Ayurvedic medicines (CG4 combination of 4 Ayurvedic drugs) from the beginning of the chemotherapy and continued for 15 days after completion of chemotherapy. CG4 is a formulation which contains a combination of 4 Ayurvedic medicines namely Mouktikayukta Kamdudha, Mauktikyukta Pravalpanchamrut, Shatavari Kalpa and Padmakadi ghruta.

**Mouktikayukta Kamdudha** –

An Ayurvedic Rasa Kalpa (herbo – mineral formulation) medicine which contains Guduchi (Tinospora cordifolia) satva as a herbal content and Shankh bhasma (Conches), Shauktik bhasma (Pearls), Kapardika bhasma (Cowries), Praval bhasma (Corals), Mouktik bhasma (Mukta) and Gairik (Red Lumber Stone) as the mineral contents.

Guduchi is having Tikta, Kashay Rasa and Madhur Vipak. It is Tridoshashamaka, pacifies three doshas. Guduchisatva is Rasayan, Agni deepan, Balya, Dahshamaka, Jwaraghna and Raktashodhak. Guduchi satva is sheeta in nature, which is the starch based preparation of Guduchi. It has cooling action. These properties of Guduchi are useful in counteracting the Pitta dominant, Raktadushtikar and Agnimandya induced symptoms as side effects of chemotherapy. It boosts the suppressed immune status with its Rasayana action.

Gairik having Madhur Ras, Madhur vipak and Sheeta virya which is beneficial in pacifying Pitta dosha. It possesses the property of Vishanashana. Thus it is beneficial in Pitta pradhan (dominant) side effects of chemotherapy such as GI bleeding, stomatitis, skin rash, hyperpigmentation, vomiting, loose motions, anorexia, nausea in breast cancer patients and eliminates toxins accumulated in the process of disease development and chemotherapy.

Praval is having Madhur, Amla, Kashay Ras, Madhur vipak and Sheet veerya. It is Pittanashak and Kaphanashak and possesses Rasayan, Jwarhar, Raktapittanashak and
Vishghna action which counteracts the chemotherapy induced side effects like anorexia, nausea, taste abnormality, vomiting stomatitis, skin rash, myelosupression. It is Raktaprasadak and helps in maintaining hemoglobin levels and other blood counts during the course of chemotherapy.

Mouktik bhasma possesses Madhur Kashay Ras, Madhur vipak, and Sheet virya. With these properties it is Balya, Tridoshshamak and Dahashamak. The chemotherapy induced side effects like anorexia, nausea, GI bleeding, vomiting, stomatitis, are thus well controlled by intake of Mouktik Bhasma.

Combination of Shankh bhasma, Shauktika bhasma and Kapardika bhasma is mainly Pachak, Tridoshshamak, Agnideepak and thus it alleviates anorexia (annanabhilasha) and vomiting (chhardi) by improving digestion. Nausea and taste abnormality developed during the course of chemotherapy are well controlled with this combination. The mineral contents of this combination are Praval, Shankha, Shauktika and Kapardika. The mineral contents of this combination are basically aquatic in nature thus having Jalamahabhuta dominance. Prithvi and Jalamahabhuta dominant contents reduce the heat (Ushna guna of vitiated Pitta Dosha) and toxicity in the body produced due to chemotherapy. Gairik, is a mineral which is Prithvi mahabhut dominant. Thus this combination is useful in counteracting the Tejamahabhut dominant side effects of chemotherapy according to one of the Ayurvedic concept ie Vishesh siddhanta.

Mouktikayukta Pravalpanchamrut is a combination of Shankh bhasma (Conches), Shauktik bhasma (Pearls), Kapardika bhasma (Cowries), Praval bhasma (Coral), and Mouktik bhasma (Mukta). The mode of action of these minerals in chemotherapy side effect is previously discussed. Godugdha is the bhavana dravya (used for trituration) used in the preparation of Praval Panchamrut which imparts the additional cooling effect to the formulation. It enhances the Pittashamaka activity and counteracts the side effects of chemotherapy.

Padmakadi Ghrut contents Padmaka (Kamal), Durva (Harali), Ananta (Sariva) and Goghruta. Padmaka, Durva, Ananta and Ghruta are having Madhur, Kashaya, Tikta Rasa, Sheeta Veerya, Madhur Vipaka due to which it is having action on doshas as
Pittanashaka, Kaphanashaka and Tridoshashamaka. It is also useful in Trushna (thirst), Mukhapaka (stomatitis), Amlapitta (Acidity) and Daha (burning).

Tikta rasa, Kashaya rasa and Madhur vipaka of Durva is useful in Agnimandya (Loss of appetite) and Arochak (Loss of appetite). It has beneficial effects on Chhardi (vomiting), Dravamalpravrutti (loose motions), Swedadhikya (excessive sweat), Raktapitta (bleeding through openings of body). Snigdha Guna of Sariva and Ghruta is useful in Agnimandya (loss of appetite), Daha (burning all over body), Malavastambha (constipation), Raktapitta (bleeding though openings of body). Varnya and ropana guna of Padmak are supposed to be useful in Twak dushti (Hyperpigmentation of skin), skin rash. Vishaghna guna of Anantomool, Padmaka and Ghruta are useful in the management of the severe toxic, side effect of chemotherapy. Deepan Karma of Anantmool and Ghruta, Raktasangrahi Karma of Padmak and Anantmool, Rasayan karma of ghruta are useful in management of Daurbalya (weakness), Bharkshaya (loss of weight).

Shatavari Kalpa contents Shatavari and sugar. Shatavari is having Madhur rasa, Madhur vipaka and sheet (cold) guna, thus possesses action as Vata-Pittashamaka, Balya, Vayasthapan, Rasayan. Netrya, Sthanyakar, Shothhar, Medhya, Hrudhya, Vrushya, Agnivardhan, With these properties it counteracts the side effects of chemotherapy.

Overall role of CG4 on chemotherapy induced side-effects is explained on the basis of Ayurvedic principles is as follows –
1. Improving digestion (Pachan)
2. Improving appetite (Deepan)
3. Anti-inflammatory (Shothaghna)
4. Pacifying vitiated Vata and Pitta Dosha
5. Detoxifies blood (Raktaprasadak)
6. Enhancing immune system (Rasayana)
7. Detoxifying (Vishaghna)
D) Discussion on management of adverse effects of chemotherapy with CG4 in breast cancer patients undergoing chemotherapy -

**Anorexia** - It is the significant side effects of chemotherapy in breast cancer. As per Ayurvedic principles, it is mainly Rasapradoshaja vikara and caused due to vitiation of Kapha and Pitta doshas. Chemotherapy hampers the function of agni. It also affects the metabolism of pachaka pitta and causes angnidushti which leads to Rasa dushti, Rakta dushhti and Rasa - Rakta kshaya. These are the precipitating factors of chemotherapy induced anorexia.

Anorexia - It can be seen that in Group A (Study group) 8 & 24 patients had Grade I and II anorexia respectively immediately after the 1st chemotherapy. While 19 & 8 patients from group B (Control group) had grade I and II anorexia. It implies grade I and II anorexia was evident in the patients of both the groups. At the end time-point (time point c) that is 15 days after the last chemotherapy, 29 patients of study group (A group) got complete relief, 14 patients shows moderate relief in anorexia. While In group B (Control group), only 18 patients got complete relief while rest of the patients were having grade II & grade III anorexia. It implies grade II and III anorexia was evident in control group patients while complete relief in anorexia or grade I anorexia were seen in patients treated with adjunct Ayurvedic treatment. This observation was statistically supported with significant p value ie p < 0.0001. These observations established the significant efficacy of Ayurvedic treatment in management of anorexia (annanabhilasha) which is caused due to agnidushti. Agnidushti is a consequence of chemotherapy induced Pittavrudhi and Raktadushti.

**Nausea (hrullas)** – It is due to the Pittaprakopa, Agnidushti (hampered digestion) and Rasadushti. It is the significant side effect of chemotherapy drugs. Pachaka pitta gets vitiated causing agnidushti and produces nausea.

16 patients from group A and 18 patients from group B were not suffering from nausea when assessed after 1st cycle of chemotherapy. At this time point, 9 patients from group A and 21 patients from group B had grade I nausea, 19 patients from group A and 11 patients from group B were having grade II nausea, 6 patients from group A had grade III nausea. At the time point c (15 days after last chemotherapy. ) nausea reduced significantly in patients of group A. 33 patients were having complete...
relief in nausea. 11, 4 and 2 patients remain in grade I, II and III respectively in group A at the end of treatment. Number of patients suffering from nausea increased to 27 and 4 respectively in Grade II and III in group B.

p value of nausea 15 days after the last chemo is also significant ie p < 0.0001 indicating effectiveness of selected Ayurvedic medicines in minimizing usha guna, pacifying Pachaka pitta and Kapha dosha and thus subsiding nausea.

**Loss of taste** - Chemotherapy induced loss of taste is developed due to Rasa dusti and Annavaha srotas dushti. According to Ayurvedic principles, Bodhaka Kapha, whose site is Jivha, is responsible for knowledge of tastes. Chemotherapy which hampers functions of bodhaka Kapha, causes loss of taste. In our study, selected Ayurvedic medicines were not found to be effective in study group. Perhaps it may be due to physiological irreversible changes in taste buds after chemotherapy.

**Vomiting** – Chemotherapy drugs mainly hamper digestion, leading to Pachaka Pitta dushti. Vomiting is induced due Pachaka Pitta dushti. Vomiting leads to severe Rasakshyaya and Agnimandya. At time point a (after 1st chemo) 8, 8, 3 patients of grade I, II and III respectively from group A were suffering vomiting, while 35 patients did not suffer from vomiting. However at time point c (15 days after last chemotherapy) 4, 4 and 1 patients respectively had grade I, II, III vomiting and 44 patients did not suffer from vomiting from group A. This indicates extremely significant effect of study medicines on vomiting (p value < 0.0001). Shankhs, Shautik, Kapardic bhasmas from Mauktikyukta Kamdudha and Mauktikyukta Praval Panchamrut are Agnideepak and Pachak. Durva Ananata, Padmaka are chhardighna Pitta shamak, and having sheeta virya, Madhur and Kashsya Rasa, Madhur vipaka which pacifies Pitta and subsides vomiting.

**Diarrhoea** - It is another severe side effect of chemotherapy that causes severe Rasa Kshaya, Agnimandhya which leads to sever weakness and giddiness. In our study, at time point a (after 1st chemotherapy) 2, 5 and 2 patients were having grade III, II and I diarrhoea from study group and 1 and 4 patients were having grade II and I diarrhoea from group B. At time point c (15 days after last chemo) 0, 1, 2 patients were having grade III, II, I diarrhoea respectively, which indicates efficacy of Ayurvedic treatment
in management of diarrhoea. On the other hand, in group B, 7 and 8 patients of grade II, I respectively were suffering diarrhoea. Among Ayurvedic medicines Kamdhudha and Pravalpanchamrut are Grahi and Stambhak in nature. Kashaya rasa and Madhur vipaka of Durva (One of the content of Padmakadi Ghruta) is useful in relieving diarrhoea. The p value <0.0001 which is extremely significant. Indicates usefulness of study medicine in management of diarrhoea.

**Gastro intestinal (GI) bleeding** – It is an another commonly observed side effect of chemotherapy. The toxicities of chemotherapy medicines increase Ushna and Tikshna guna in body, which causes severe irritation and ulceration in the GI tract. Padmaka, Ananta, Durva and Shatavari possess Sheeta virya, Madhur vipaka and Madhur, Kashaya Rasa which helps to control bleeding. These medicines are also Vranaropak (possess healing property) in nature. Study group patients responded well to GI bleeding (p=0.00488).

**Stomatitis** – Not quite significant results of Ayurvedic medicines were found for stomatitis in our study.

**Constipation** is relieved significantly as compare to control group. Mauktikyukta Kamadudha and Mauktikyukta Pravalpanchamrut, Padmakadi ghruta pacify Pitta and Vata dosha. These drugs also possess Deepana and Pachana property. Thus constipation caused due to excessive ushna and ruksha guna, was well controlled with these medicines.

**Alopecia** – Extremely significant results were observed in alopecia. This is due to the fact that maximum number of patients from group A received Paclitaxel, Carboplatin regimen, which is not likely to cause Alopecia.

Skin rash, hyperpigmentation, photosensitivity and nail discoloration – Very less number of patients in both the groups presented with these symptoms. Thus statistical analysis was not possible for these symptoms.
E) Discussion on clinical parameters (Karnofsky score and QLQ) assessed in breast cancer patients treated with chemotherapy

In this study, we assessed the patient’s response to treatment in terms of functional ability and global status with the help of QLQ of EORTC and Karnofsky scores which are well-accepted methods of analysis of outcome measures.

Karnofsky score for performance status was recorded for assessment of general wellbeing and ability to conduct activities of daily life. The higher score of Karnofsky denotes better ability to carry on normal activity which was recorded in Oxford Textbook of Palliative Medicine.

As Karnofsky score indicates feeling of wellbeing. It commonly shows decreasing trend during the course of chemotherapy. As per this trend Karnofsky score of most of the patients in control group was remarkably declined after 1st chemotherapy, in the middle of chemotherapy and 15 days after completing chemotherapy (80, 69, and 67 respectively). On the other hand Karnofsky score was not significantly reduced at the three time points in study group (84, 80, 76 respectively), indicative of beneficial effects of adjunct oral Ayurvedic medicines. Karnofsky score shows $p<0.0001$ (extremely significant), $p=0.0006$ (extremely significant) when tested in middle of the chemotherapy and 15 days after completion of chemotherapy.

The Quality of Life (QLQ) is assessed on the basis of 3 parameters ie functional score, global score and symptom score as per EORTC QLQ - C30. Functional score is the sum total of improvement in all side effects of chemotherapy leading to achieving normal levels of functional ability of the patient, which is end point of assessment of well-being of the patient. It is a numerical score. Increase in the score denotes improvement in general functional activity of the patient.

The Global score denotes status of QLQ as judged by the patient himself. Improvement in global score indicates improvement in QoL. Symptom score indicates sufferings or symptoms. Higher symptom score indicates severe symptom gradations. Functional score and Global score of QoL (quality of life) are normally hampered after completion of chemotherapy. In our study decreased functional and symptom scores were observed in almost all patients in control group, while these
parameters were improved or maintained in nearly 42 patients of study group. This indicates effectiveness of selective Ayurvedic medicines in boosting immunity due to their Rasayana action, decreasing symptomatology and ultimately improving functional ability of patients during and after chemotherapy. Global score of QLQ is very significant at time point b (p=0.0008) and extremely significant at time point c (p < 0.0001). There is no statistical improvement seen in functional and symptom score as the functional improvement after chemotherapy is rather slow and in symptom score the discrepancy could be due to less improvement in disease related symptoms.

**F) Discussion on pathological investigations assessed in breast cancer patients treated with chemotherapy**

Myelossupression is the known side effect of chemotherapy. The hemoglobin percentage and the WBC count show no change in both the groups. Platelet count is extremely significant at time point b (p < 0.0001). A set of Ayurvedic medicines used in the study was not effective in treating chemotherapy induced myelosupression, though its efficacy is proved in management of major side-effects of chemotherapy.