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Eclipta alba Extract with Potential for Reversing Chemotherapy-induced Alopecia: An Experimental Study in Mice

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ABSTRACT

Chemotherapy-induced alopecia (CIA) or scalp hair loss is a well known adverse effect of conventional anticancer drugs like alkylating agents. Presently, there are no drugs which when given alongwith anticancer chemotherapy can be used for the treatment of CIA as preventing or reversing agents.

The whole plant extract of *Eclipta alba,* Hassk (Family Compositae) commonly known as Bhringraja, when used as oil applied topically on head has been reported to promote scalp hairs. In the present study ethyl acetate fraction (EAF) of methanolic extract of *Eclipta alba* has been investigated for hair growth promoting effect in a mouse model where alopecia-like state was produced by systemic administration of a cytostatic alkaylatic agent, etoposide. Etoposide was administered in a dose of 36 mg/kg, i.p. using two strains of mice: Swiss albino (with white body hairs) and C57/BL6 (with black body hairs) to inhibit the normal hair growing activity in a shaved area of skin 4x4 cm (4 cm^2) on the dorsal (back) surface of the trunk in groups of each species of mice. EAF or its vehicle was applied topically in the form of cream on the shaved area of skin of different groups of mice in two concentrations: 1.6%

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and 3.2%. Initially, some pilot experiments were conducted to generate the baseline data related to morphological and histological changes in shaved area of skin at different time points. Histopathological studies were conducted on skin section for hair growth activity in both strains of mice. In each strain of mice after recording the morphological changes for hair growth activity, the animals were sacrificed under deep ether anaesthesia on day 0, 1, 7, 11, 14 and 16 for recording microscopic histological changes in the transverse and longitudional sections of skin for skin thickness and hair follicle growth activity. The animals were photographed on different days and the evaluation of morphological changes were recorded by a blind observer for hair growth activity in the shaved areas and the alopecia was graded and scored by standard prescribed methods. The main study was conducted in seven groups of six animals each for obtaining the morphological and histological data of various groups treated with two doeses of EAF and the vehicle with or without administration of etoposide or its vehicle in doses as described above.

Results of morphological hair growth showed that the mice treated with etoposide-induced 100% inhibition of hair growth (considered as alopecia) during a span of subsequent 30 days post-treatment period. Topical application of EAF cream in the administered concentrations produced a dose-dependent reversal of inhibition of hair growth produced by etoposide, whereas EAF vehicle applied topically as cream failed to show any such activity. The results demonstrated that EAF of *Eclipta alba* has a potential to reverse the inhibition of etoposide-induced hair growth in both strains of the study mice.

Keywords: Anticancer chemotherapy, alopecia, chemotherapy-induced alopecia (CIA), etoposide, hair growth.

Introduction

Eclipta alba, Hassk (Bhringaraja, Family: Compositae) has been traditionally used to check hair loss and stimulate hair growth (1). The plant is a small-branched annual herb with white flower heads inhabiting tropical and subtropical regions of the world. The extracted juice, if taken internally and applied to the scalp blackens the hair and has been reported to promote hair growth when used as part of several polyherbal formulations

(1-4). The reported hair growth promoting activities of *Eclipta alba* in traditional and published literature prompted us to explore this plant extract for reversing chemotherapy-induced alopecia (CIA) in an experimental model in mice.

Alopecia

Alopecia stands defined as hair loss and is a common human affliction resulting from changes in hair follicles or hair cycle or a combination of both (5, 6). Human hair represents an ensemble of some 10^5 hair follicles that continually evolve over the course of time. At any time, a follicle is either growing (anagen phase) or ceasing to grow and involuting (catagen phase) but still on the scalp (telogen phase) before shedding and entering a new cycle (7). These successive phases constitute a follicular cycle. The duration of such a cycle is variable but typically ranges from a few months to several years. Each follicle can undergo repeated cycles until it eventually dies or miniaturizes to give rise to a vellus hair; the vellus hair shaft is not pigmented and has a cross-sectional diameter much thinner than normal. Whether miniaturization occurs progressively or abruptly is still unclear. If large proportions of follicles die or miniaturize, alopecia ensues, with a severity that depends on the location of lost follicles and on the amount of total hairs that are irreversibly shed (8).

Chemotherapy-induced Alopecia (CIA)

CIA is one of the most common side effects of anticancer chemotherapy employing cytotoxic and cytostatic agents (9, 10). CIA could be a cause of a stigma, which, in its metaphorical term, is referred to as discrediting attribute that may be physical, behavioural or biogeographical. CIA is ranked third in the list of distressing symptoms for cancer patients after nausea and vomiting (11). The adverse effect of cancer chemotherapeutic agents can manifest as thinning of hair, partial loss of hair or complete loss of hair leading to baldness (alopecia). Hair loss usually happens 2-3 weeks after the start of treatment with chemotherapeutic agent(s) or cycles of treatment. Sometimes it starts within a few days and then tends to increase 1 to 2 months into treatment. Several factors may contribute to the severity of the hair loss. The extent of hair loss depends on the type of the drug or the combination of chemotherapeutic agents, the dose of

the drug(s), root of administration (oral, I.V., I.M. or in the skin) and sensitivity of the individual to the drug (5, 11, 12).

Most drugs used in cancer chemotherapy affect the growth and metabolism of not only malignant cells but certain normal tissues as well. Tissues with rapid metabolic and mitotic rates such as the roots of scalp hair are most noticeably affected (13). Ninety percent of all the scalp hair follicles are in a phase of rapid growth and the high blood flow rate around the hair bulbs results in an optimal bioavailability of many compounds to this area (14). The majority of the cancer therapeutic drugs that cause hair changes such as alopecia are alkylating agents, vinca alkaloids, antimetabolites, anthracyclin antibiotics (doxorubicin), platinum-based drugs (cisplatin, carboplatin), taxoids (docetaxel, paclitaxel), as well as some of the new classes of drugs called targeted therapeutic agents (15). However, the last class of drugs (cetuximab, afatanib, dabrafenib, dasatinib, erlotinib, ibrutinib, imatinib, nilotinib, panitumumab, trametinib, sorafenib, vemurafenib, sonidegib, vismodegib, etc.) may cause the hair loss to thin or to become curlier and drier than earlier, rather than the frank loss of hairs or dopecia.

Therapeutic Challenges of Developing Drugs for CIA

Till date there is no approved drug against CIA. During the situation of anticancer chemotherapy the main focus of the oncologist is the treatment of cancer and prevention of its metastasis. Further, it is thought that during the remitting period when anticancer drugs are no more given, the CIA may recover by its own. As a result not much efforts have been made in the past to study drugs which can prevent or decrease/ delay the progress of CIA even during the use of anticancer chemotherapy. With this background, in the present study, we have explored a number of plants as a source for identification of new medicaments with hair growth promoting activities, which is much safer for the humankind in clinical settings of anticancer chemotherapy.

The present investigation deals with a part of this ongoing work where the role of *Eclipta alba* plant extract has been investigated in two strains of mice which were challenged with etoposide, an anticancer cytostatic agent for inhibiting the growth of shaved hairs giving a simulation to producing CIA.

Materials and Methods

Animals and Animal Care

Two strains of healthy Swiss albino (with white hairs) and C57/BL6 (with black hairs) mice were purchased from National Institute of Nutrition (NIN) Hyderabad (India) and fed with standard rat chow and water *ad libitum.* Animals were housed in polypropylene cages maintained under standard conditions of 12-hour light/dark cycle and 23± 2ºC with 35-60% humidity. All mice were kept in quarantine for one week prior to experimentation. All experiments were carried out according to the guidelines laid by Institutional Animal Ethics Committee (IAEC) of Dabur Research Foundation, India.

Chemicals

Propylene glycol was obtained from Spectrochem Pvt. Ltd., India. Sodium Chloride injection was obtained from Parth Parenteral Pvt. Ltd., India. Etoposide was purchased from Dabur India Ltd. Methanol, ethanol, ethyl acetate, benzyl alcohol, dehydrated alcohol, polysorbate 80 and formaldehyde were obtained from Merck, Germany.

Fractionation and Sub-fractionation of the Extract

Dried *Eclipta alba* whole plant was procured from the Ayurvedic store of Dabur Research Foundation and the Agro-technologist of Research Foundation authenticated the sample. A voucher specimen was preserved with the Ayurvedic Division of Dabur Research Foundation.

An amount of 1000 g of the shade-dried whole plant powder of *Eclipta alba* was initially extracted in 95% methanol using soxhlet. The methanolic extract was filtered and concentrated under reduced pressure to provide a 100 g crude extract. This extract was suspended in de-mineralized water and heated on water bath at 60°C to remove wax like matter. After filtration, water phase was partitioned with chloroform followed by ethyl acetate. The ethyl acetate fraction (EAF) was filtered and dried using sodium sulphate and vacumm, leaving 5.8 g of light brown powder. The final EAF of methanolic extract found to be rich in coumestans was screened for hair growth promoting activity.

Evaluation of Etoposide-induced Alopecia in Adult Swiss Albino and C57/BL6 Mice

Based on the principle that follicles in telogen phase can be induced to enter the anagen phase by mechanical traumatization (16), such as shaving (17), a method was developed which served as a model for studying etoposide-induced alopecia.

This *in-vivo* model for etoposide-induced alopecia and screening of EAF was used in both adult Swiss albino and C57/BL6 mice. Forty five to 60 days old male mice of both the strains were used in the study. On day zero, not more than 10% of the body hairs, i.e. from an area of 4x4 cm (4 cm^2) of the dorsal surface were shaved off using sterile scalpel blade and care was taken not to cause nick or abrasion to the underlying dermal layer.

For generating the baseline data, some pilot experiments were coducted in groups of both strains of mice: Swiss albino and C57/BL6 mice which were sacrificed under deep ether anesthesia on day 0, 1, 7, 11, 14 and 16 day post-shaving. Skin specimens were taken from the shaved skin of areas on the dorsum (back) of the trunk and processed for histological evaluation in both longitudinal and transverse sections. The follicles in the subcutis were counted as an indication for anagen induction. The animals were photographed on different days and the evaluation of morphological changes were documented by a blind observer for hair loss and hair growth. Induction of alopecia was graded as per method described by Hussein *et al* (18) (Table 1).

Table 1: Scoring scale for alopecia-induced by etoposide

Scale	Description
0	No detectable alopecia
1	Mild alopecia defined as less than 50% hair loss
2	Moderately severe alopecia with more than 50% hair loss
3	Total absence of hair

To study etoposide-induced alopecia or decrease in the hair regrowth, the etoposide and the vehicle for etoposide was administered intraperitoneally (i.p.) on 9th, 11th and 13th day of post-shaving period in different groups of both the strains of mice (Table 2).

Table 2: The treatment groups in etoposide-induced alopecia model

Group No.	Days of treatment	Treatment	Dose/Day	
			Etoposide	Vehicle
I	9^{th} to 14^{th}	Untreated	Nil	Nil
II	9^{th}, 11^{th}, 13^{th}	Vehicle of Etoposide injection	Nil	Equivalent dose with respect to highest dose
III	9^{th}, 11^{th}, 13^{th}	Etoposide	36 mg/ kg (i.p.)	Nil

Evaluation of EAF on Etoposide-induced Alopecia

The main study was conducted in seven groups of six animals each. Treatment was given to six different groups of both strains of animals as shown in Table 3. The EAF effect was evaluated in two concentration doses: 1.6 mg/4 cm^2 and 3.2 mg /4 cm^2 in both strains of mice groups. The composition of vehicle for etoposide was benzyl alcohol (30 mg), dehydrated alcohol (30.5%v/v) and polysorbate 80, whereas the composition of vehicle for EAF was propylene glycol (93%), glycerol (3.5%) and DMSO (3.5%). Etoposide (36 mg/kg, i.p.) or its equivalent amount of vehicle was administered in the indicated dose by i.p. route, whereas EAF was applied topically in the form of cream to observe the hair growth promoting activity and effect in the shaved area on the dorsal surface of the animal's trunk. At the end of the study, the group of mice were photographed and observations were documented by a blind observer as per scale of hair loss or scale of hair growth. Induction of alopecia was graded using Hussein *et al* method (18) (Table 1), while the scale of hair growth was scored following the method of Steiner and Hamilton (19) (Table 4). Before submitting the skin from the experimental area of 4 cm^2 for making sections for histopathological microscopy, the regrown hairs were shaved off and weighted on a precision one-pan balance for the quantitation of hair regrowth which was expressed as hair weight in miligram (mg) for comparison of the regrown hair data among different groups of mice.

Statistical Analysis

All the study parameters were expressed as Mean±SEM in their respective units and the obtained data were analyzed using SAS version 9.1.3. The level of statistical significance was considered at 'p' value < 0.05.

Table 3: Treatment schedules in different groups of animals for screening of EAF in different group of mice

Group	Days of treatment	Treatment	Dose			
			Etoposide (mg/kg; i.p.)	EAF mg/ 4 cm^2 (topical)	Vehicle for etoposide (i.p.)	Vehicle for EAF (topical)
I	9^{th} to 15^{th}	No treatment	Nil	Nil	Nil	Nil
II	9^{th}, 11^{th}, 13^{th}	Vehicle for etoposide	Nil	Nil	Equivalent volume	Nil
III	9^{th} to 15^{th}	Vehicle for EAF	Nil	Nil	Nil	Equivalent dose with respect to highest dose
IV	9^{th}, 11^{th}, 13^{th}	Etoposide	36	Nil	Nil	Nil
V	9^{th}, 11^{th}, 13^{th}	Etoposide and EAF	36 (Administered after one hour of EAF)	1.6	Nil	Nil
	10^{th}, 12^{th}, 14^{th}, 15^{th}	EAF	Nil	1.6	Nil	Nil
VI	9^{th}, 11^{th}, 13^{th}	Etoposide and EAF	36 (Administered after one hour of EAF)	3.2	Nil	Nil
	10^{th}, 12^{th}, 14^{th}, 15^{th}	EAF	Nil	3.2	Nil	Nil
VII	9^{th}, 11^{th} 13^{th}	Etoposide and EAF vehicle	36 (Administered after one hour of EAF (vehicle)	Nil	Nil	Equivalent dose with respect to highest dose
	10^{th}, 12^{th}, 14^{th}, 15^{th}	Nil	Nil	Nil	Nil	Equivalent dose with respect to highest dose

Table 4: Scoring scale for hair growth as per method used by Stiener and Hamilton (19)

Scale	Description
0	No growth
1	Beginning of growth in small tufts
2	Hair growth covering over < 25% of shaved area
3	Hair growth covering over > 25% but less than 50% of the shaved area
4	Hair growth covering over > 50% but less than 75% of the shaved area
5	Complete hair growth of shaved area

Results

Baseline Data

The histopathological evaluation was conducted on hematoxylin and eosin stained transverse sections of the cut skin specimens obtained from the respective experimental groups of animals. The changes in the skin thickness and the number of follicles in the subcutis on day 0 and on 1st, 7th, 11th, 14th and 16th day of post-shaving period were counted as an indication for anagen induction. The histopathological changes clearly indicated that there was a significant increase in the skin thickness and follicle counts in the subcutis. The consolidated results have been tabulated for Swiss albino mice and C57/BL6 mice in Table 5, 6a and 6b.

Histopathological data from the transverse sections show that the animals at 13 or 14 days of post-shaving period were in active proliferative phase, i.e. anagen phase of hair growth, characterized by an increase in skin thickness. The increase in thickness of subcutis placed just above panniculus carnosus and an increase in follicle count in subcutis layer was observed in both strains of mice. Additionally in C57/BL6 mice, there was an increase in the melanogenesis as evident in resected skin and punch biopsies. Animals at day 0-, 1-, 7-, 11- and 16-day post- depilation were at quiescent phase (telogen phase). However, 14-day post-depilated mice having hair growth at peak anagen phase of hair cycle were preselected for the evaluation of the effect of EAF for reversing or preventing etoposide-induced inhibition of hair regrowth. It was evident from the longitudinal section that during anagen phase of hair growth, hair bulb penetrates into subcutis layer (Fig. 1). The study was repeated thrice with similar results.

Table 5: Histopathological evaluation of follicle count and skin thickness in Swiss albino mice on day 0 and other post-shaving days

S.No	Days post depilation	Mean follicle count *	Mean follicle count in subcutis layer *	Average skin thickness (μm) *
1	0	11.5 ± 0.5	0	244.00 ± 15.27
2	1	14.0 ± 1.0	0	289.02 ± 28.15
3	7	30.5 ± 3.5	5.5 ± 5.5	296.11 ± 24.03
4	11	87.0 ± 5.0	70.0 ± 4.0	491.51 ± 38.6
5	14	113.0 ± 0.0	95.5 ± 1.5	638.69 ± 32.5
6	16	64.5 ± 0.50	41.5 ± 1.5	391.31 ± 9.14

* Mean ± SEM.

Table 6a: Histopathological evaluation of follicle count and skin thickness in C57/BL6 mice on day 0 and relative post-shaving days

S.No	Days post depilation	Mean follicle count *	Mean follicle count in subcutis layer *	Average skin thickness (μm) *
1	0	20.5 ± 7.5	0	388.9 ± 59.30
2	1	28.0 ± 6.0	0	380.0 ± 57.99
3	7	24.5 ± 5.50	0	383.0 ± 45.15
4	11	45.5 ± 4.5	17.5 ± 2.25	580.07 ± 8.00
5	14	86.0 ± 4.0	52.0 ± 4.5	666.51 ± 12.40
6	16	37.0 ± 1.0	7.0 ± 0.35	457.53 ± 43.60

* Mean ± SEM.

Etoposide-induced Alopecia

The results of both strains of mice: Swiss albino and C57/BL6 mice have been shown in Fig. 1, 2 and 3, respectively. Observations of alopecia/ hair growth revealed that the treatment of Group IV animals with etoposide-induced 100% visible alopecia. Onset of alopecia was seen in all the animals in Group IV on day 18 of the experiment and complete alopecia was documented in this group till 30 days post-treatment, whereas normal hair growth was seen in Group I, II and Group III animals during the period of 18 - 21 days post-treatment (Table 6b).

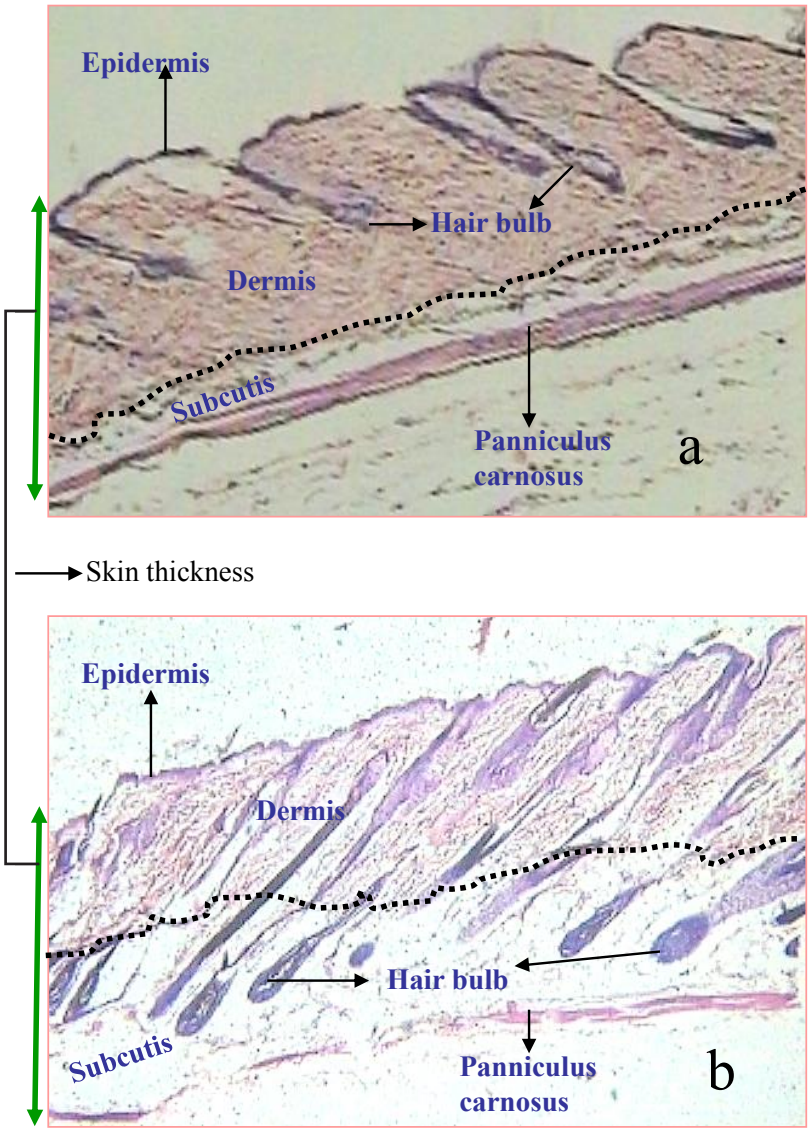


Fig. 1: Hair growth cycle in C57/BL6 mice-post birth.

a) Longitudinal sections of skin of animals in telogen phase of hair growth (0,7, 11 and 16 day old). The hair bulb is shrunken and is present in the dermis above the subcutis layer.

b) Longitudinal sections of skin of animals in anagen phase of hair growth (14 day old). The hair bulb is rigid and is present deep in the subcutis layer.

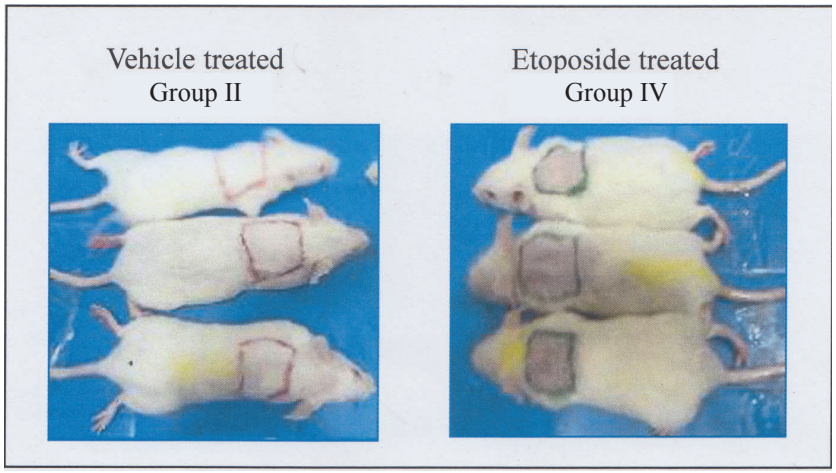


Fig. 2 : Induction of etoposide-induced alopecia in adult Swiss albino mice

On 21st day the scale of growth in etoposide treated group is zero as compared to vehicle treated group where scale of hair growth is 5.

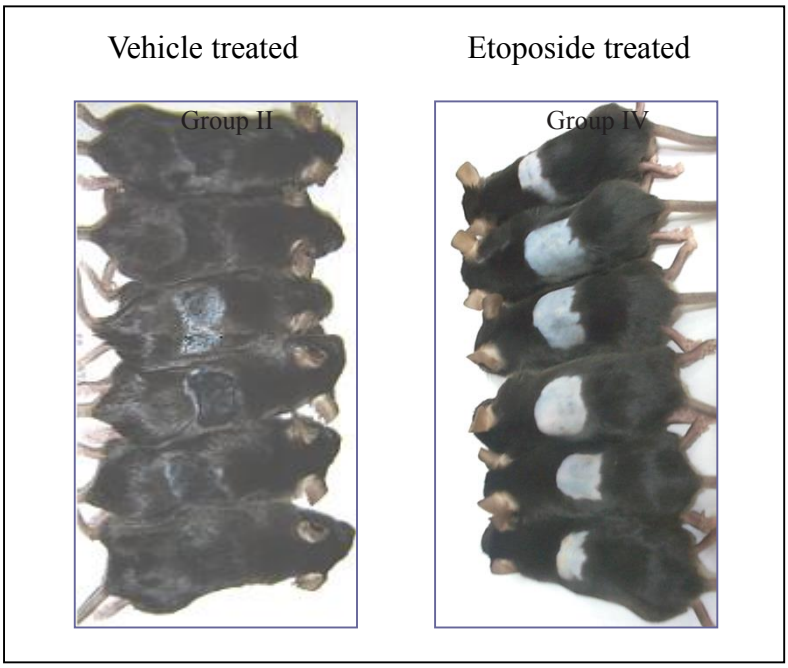


Fig. 3 : Induction of etoposide-induced alopecia in adult C57/BL6 mice.

On 21st day the scale of growth in etoposide treated group is zero as compared to vehicle treated group where scale of hair growth is 5.

Protective Effect of EAF

The hair growth was evaluated every day by the blind observer and documented for day 18, 19, 20, 21 and 30 after treatment. After the treatment with EAF, the quantitation of alopecia/ hair regrowth was expressed as percentage of shaved area covered by new hair growth, scored by blinded observer on a scale of 0 as no hair growth to 5 as complete hair growth. The data on hair growth after the treatment with EAF are presented in Table 6a and b.

Table 6b: Analysis of Scale of hair growth in adult Swiss albino and C57/BL6 mice after treatment with EAF

Days	Group I	Group II	Group III	Group IV*	Group V*	Group VI*	Group VII*
Alopecia %/ Hair growth on indicated days							
18th Day	Normal hair growth	Normal hair growth	Normal hair growth	0-10 alopecia	0-10 alopecia	0-10 alopecia	0-10 alopecia
19th Day	Normal hair growth	Normal hair growth	Normal hair growth	10-40 alopecia	10-40 alopecia	10-40 alopecia	10-40 alopecia
20th Day	Normal hair growth	Normal hair growth	Normal hair growth	40-80 alopecia	40-80 alopecia	40-80 alopecia	40-80 alopecia
21st Day	Normal hair growth	Normal hair growth	Normal hair growth	100 alopecia	100 alopecia	100 alopecia	100 alopecia
Hair growth score on indicated days							
30th Day	5	5	5	0	2	5	0

* Data shown is % alopecia or hair regrowth on different days (18th to 21st).

Table 7: Effect of EAF at a concentration of 3.2 mg/4 cm^2 on morphologically selected telogen skin of C57/BL6 mice for hair growth promoting activity

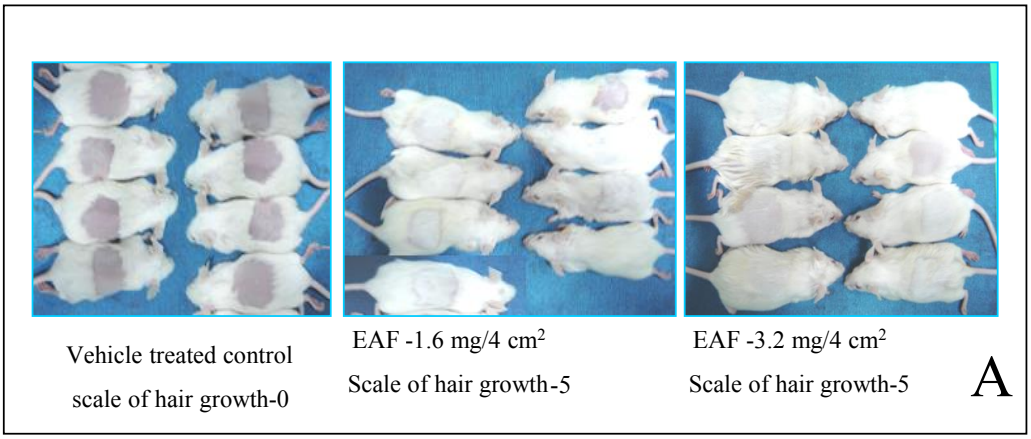
S. No	Treatment	Mean follicle count*	Average skin thickness (µm) *	% Anagen Induction	P value	Mean follicle count in subcutis layer*
1	Vehicle for EAF	19.12 ± 3.0	265.50 ± 11.92	0.0	-	0.0
2	1.6 mg/4 cm^2 of EAF	39.00 ± 8.34	417.39 ± 35.87	50.0	<0.0001	21.00 ± 8.31
3	3.2 mg/4 cm^2 of EAF	66.00 ± 7.31	480.38 ± 41.22	87.5	<0.0001	45.00 ± 7.37

*Data is presented as Mean ± SEM.

Increased hair growth was observed in Group VI animals of both strains (Fig. 4 and 5), which were treated with the higher dose (3.2 mg/cm^2) dose of EAF alone or alongwith etoposide as compared to Groups IV and VII (that received etoposide alone or etoposide plus vehicles, respectively), where scale of growth observed was 0; whereas in Group V, animals of which were exposed to the lower dose of EAF alongwith etoposide, the scale of hair growth observed was 2. A statistically significant anagen induction of 50% and 87.5% was observed in Group V and VI, respectively (Table 7). The observations obtained from animals in Group V and Group VI indicate stimulation of hair growth on treatment of topical application with EAF in two concentrations in skin but treated systemically with etoposide. All the animals in Groups I, II, III showed similar hair growth as observed in animals of Group VI (Fig. 6), where histopathological observations from transverse section of skin taken from C57/BL6 mice have been shown.

Discussion

CIA is a frequent and emotionally distressing side effect of cancer chemotherapy for which currently no effective preventive therapy is available (20, 21). CIA is thought to occur when anticancer drugs ablate the proliferating epithelium and block normal maturation of precursor epithelial cells to the final hair strand. The sensitivity of hair



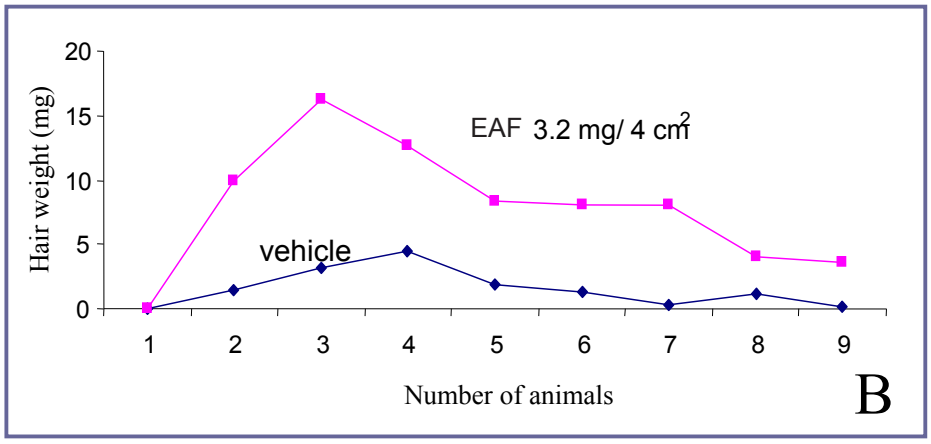


Fig. 4 : Efficacy of EAF on etoposide-induced alopecia in adult Swiss albino mice.

A. Pictures of animals treated with vehicle and EAF on 30th day of the treatment.

B. Comparative graph of hair weight in different treatment groups.

follicle cells to anticancer agents is related to their state of proliferation. Many anticancer agents that cause CIA in target specific phases of the cell cycle and are therefore selectively toxic to tissues undergoing cell division (22, 23). In a recent review of 38 articles, authors consistently concluded that the hair loss ranked amongst the most troublesome side effects experienced by patients undergoing anticancer chemotherapy for breast cancer (24). In a study by

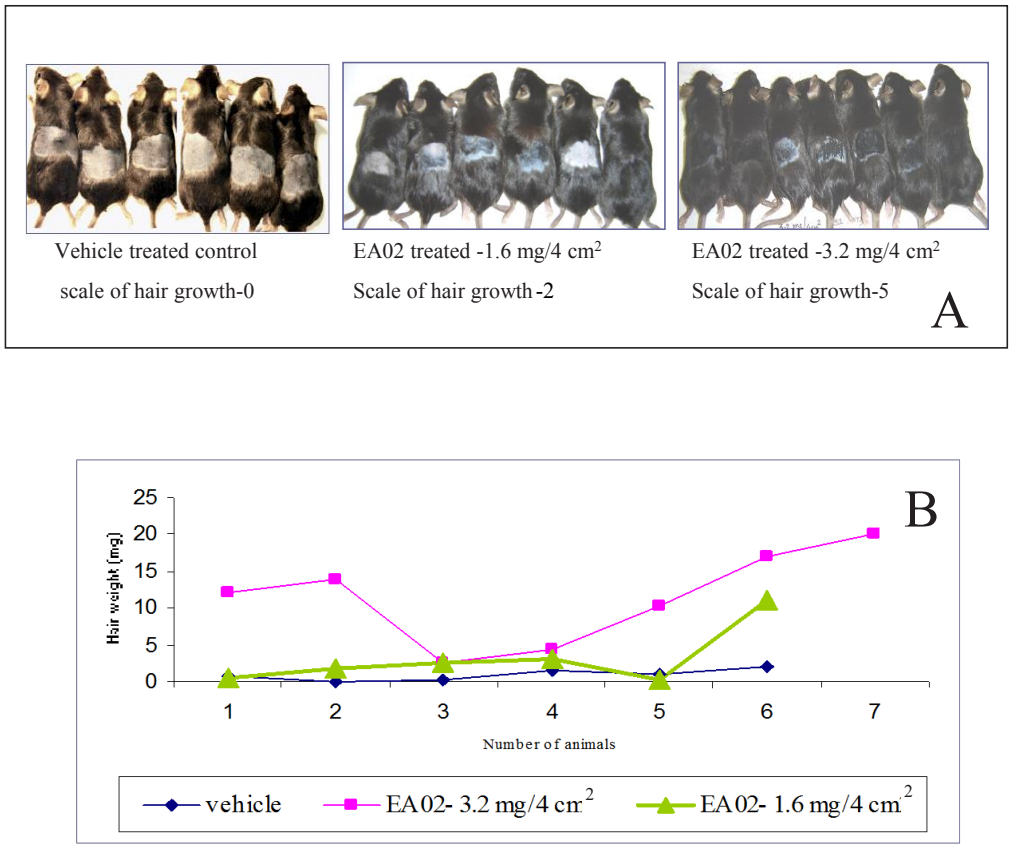


Fig. 5 : Efficacy of EAF on etoposide-induced alopecia in adult C57/BL6 mice.

A-Scale of hair growth observed in animals treated with vehicle and EAF at a concentration of (3.2 mg/4 cm^2) on 30th day of treatment.

B-Comparative graph of hair weight in different treatment groups.

Tierney *et al,* 35 of 46 patients receiving chemotherapy ranked alopecia as a more important side effect than vomiting (25). A systematic review of 10-year data on randomized controlled trials on breast cancer treatment, the incidence of alopecia was a noted adverse event (26). In 19 anti-cancer drug therapy regimens that had 95-100% of the patients suffering some degree of alopecia (grades 1-3), the common alopeciogenic agents were doxorubicin, docetaxel, epirubicin and

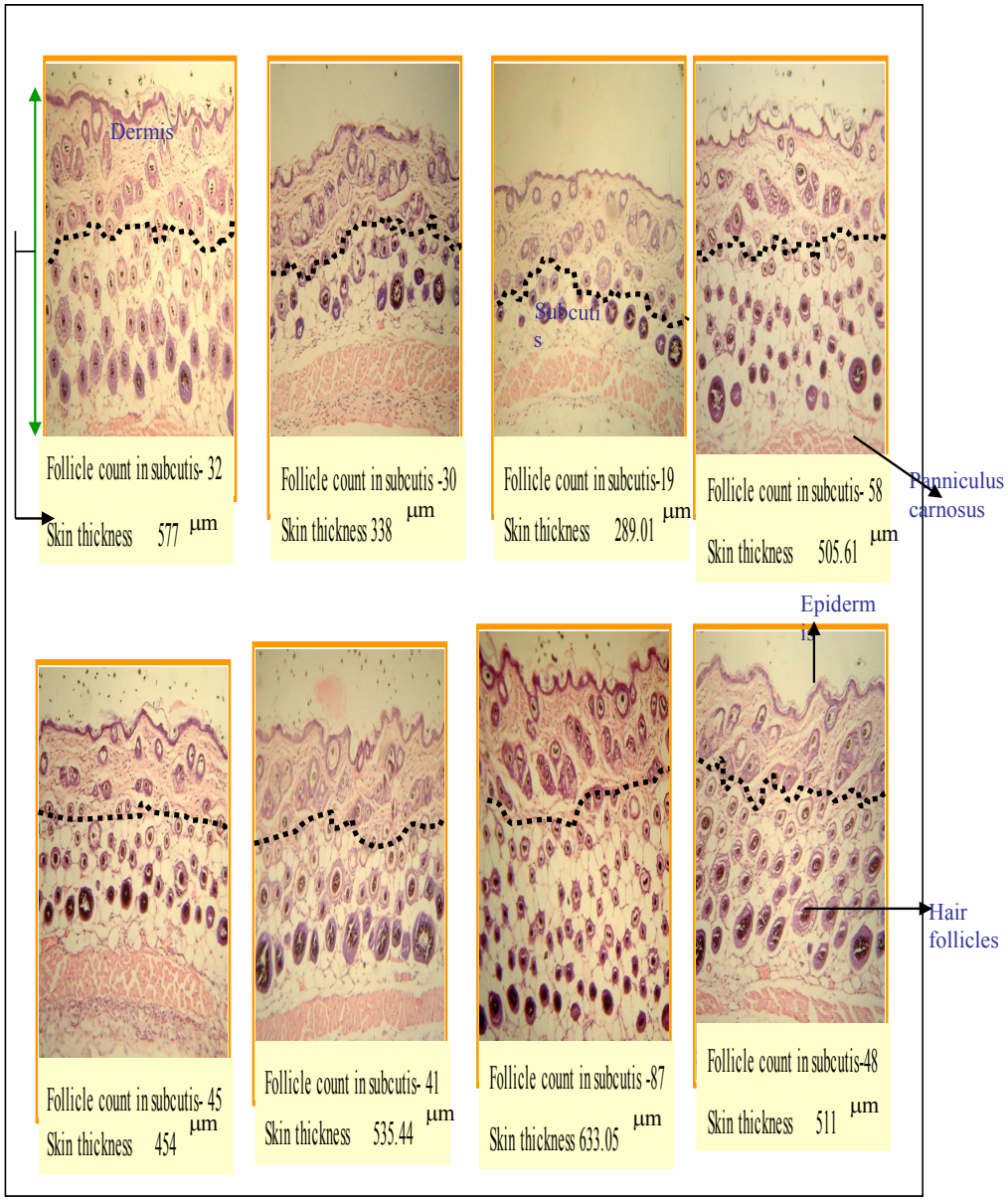


Fig. 6 : Dotted line indicates the junction of dermis and subcutis. 87.5% animals treated with 3.2 mg/15 cm^2 of EAF show telogen to anagen transition.

TS of skin showing hair growth promoting activity in C57/B26 mice treated with EAF in a concentration of 3.2%/15 cm^2.

platinum drugs, which are the main chemotherapeutic agents for solid cancers (27).

Hair regrowth after chemotherapy can take from 3 to 6 months to recover, and a small percentage of patients fail to experience complete recovery (27). CIA is particularly devastating because it is an outward sign of an otherwise hidden disease, leading some patients to refuse systemic anticancer chemotherapy (28). Methods currently utilized to prevent CIA are unsatisfactory, e.g. in two studies on randomized trial with local application of minoxidil in 48 patients in one study (29) and six evaluable patients in the second study (30) did not find it to be effective in preventing the CIA (29, 30). Therefore, it is important to investigate the CIA in appropriate experimental models that allow examination of pathobiology as well as the exploration of new strategies for its management. Two models which have been widely reported for the study and pharmacological manipulations of CIA are: models using both the neonate and adolescent mice in the situations of alopecia occurring both normally as well as in disease states. The latter model strikingly mimics the characteristic hair follicular pathophysiology during drug-induced alopecia.

The murine model allows the study of the effects of chemotherapy on well-defined, homogeneous and mature population of precisely the type of hair follicles that are severely damaged by chemotherapy, resulting in alopecia and disturbance in hair growth. The murine model also allows as yet unparalleled insights into the basic pattern of hair follicle response to recovery from chemotherapy, which is further based on the high degree of hair cycle synchrony displayed by the mouse strain. It has been reported that ImuVert, a biological response modifier prepared from the bacterium *Serratia marcescens,* protected the animals from alopecia-induced by cytosine arabinoside (31). In subsequent studies, similar protection from cytosine arabinoside-induced alopecia was observed with recombinant interleukin-1 β and later with epidermal growth factor and fibroblast growth factor (32). However, when used under similar conditions none of these agents offered protection from alopecia-induced by cyclophosphamide (Cytoxan). In the clinical setting, chemotherapy more often involves the use of alkylating agents. Accordingly, we continued our efforts to explore various compounds in the mouse model and ways to prevent alopecia from alkylating agents like etoposide.

The results of the present study clearly demonstrate that the murine model used for CIA resembles the clinical situation more closely than any other currently available experimental models for this clinical entity.

Development of *in vivo* model for etoposide-induced alopecia included generation of baseline as well as post-depilation data in Swiss albino and C57/BL6 mice. Animals at 14-day post-depilation that were in active anagen phase were selected for screening the EAF for reversing etoposide-induced decrease in hair growth. Etoposide was observed to terminate the anagen phase prematurely and caused severe decrease in hair regrowth.

The results of the present study have demonstrated that the topical application of EAF accelerated the anagen phase of hair growth in etoposide-induced alopecia, unlike the challenging agent which induced alopecia. Further, EAF accelerated normal pigmentation of regrowing hair shafts and retarded the occurrence of etoposide-induced alopecia and diminished the severity of hair regrowth. These results and the used model strongly encourages one to explore and develop extracts of the plants claimed in traditional system of medicine for enhancing the hair growth and find out the active principles there in as drugs for accelerating and improving the clinically and psychologically important regrowth of a normally pigmented hair coat after CIA in human subjects.

The novel strategies for the therapeutic management of CIA should more systematically take into account that, like the vast community of patients with abnormal hair loss or gain seen in clinical practice, CIA and its subsequent hair regrowth predominantly reflect defined alterations of normal patterns of hair follicle cycling, rather than of hair shaft production. This implies that real progress in the prevention and treatment of CIA can only be accomplished by understanding the molecular interactions of alopecia reducing agents.

In the end it is pertinent to mention that for evaluating the safety of EAF, acute toxicity studies were performed in Swiss albino mice in accordance with OECD guidelines and the resulting hematological, biochemical and all pathological findings were within normal limits after topical application of EAF as per doses and schedule of treatment used in the present study.

Based on the above observations, the

EAF of *Eclipta alba* has a potential for not only the hair growth stimulation but also preventing the CIA, as exemplified by the reversal of inhibition of hair growth by etoposide in both strains of mice.

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Economic Disparity and Mental Health

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ABSTRACT

Economic disparity is an important issue worldwide, with adverse consequences on physical and mental health of the impoverished. All over the world, the gulf between the rich and poor is widening not only between countries, but also within countries. Poverty not only increases the risk of mental illnesses, but is also a consequence of the same. This review presents a conceptual framework for understanding the relationship between mental health and economic disparity. Various studies have shown a significant relationship between low educational status, unemployment and mental illnesses. Low socio-economic status in women and children has been found to increase their vulnerability to developing mental illnesses. Possible ways of tackling the issues at different levels like at the state, inter-sectoral and research are discussed.

Keywords: Economic disparity, poverty, mental illness, psychiatric disorders, socio-economic status, low education, unemployment.

Introduction

Economic disparity refers to the differences in the economic status between different socio-economic strata in a society. It could be the differences between different strata within a society or between different countries. It is now well recognized that the gulf between the rich and the poor of the world is widening (1). Economic disparity is closely related to poverty. Over the years, research has consistently shown

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that poverty and economic disparity have direct as well as indirect effects on social, mental and physical health of individuals (2). Extreme poverty is the world's most ruthless killer and the greatest cause of suffering on earth. Poverty is associated with reduced life expectancy, handicap, disability and starvation, and has been identified as a major contributor to mental illness, stress, suicide, family disintegration and substance abuse (3). High level of income disparity reduces social capital, and may lead to rich withdrawing social support and also promotes comparison which in turn increases stress levels substantially (4, 5).

Factors like insecurity, hopelessness, inability to respond to rapid social changes, risks of violence and physical ill-health explain the greater vulnerability of the poor to common mental disorders. On the other hand, the economic costs of ill-health tend to worsen the economic condition of the individual; hence creating a vicious cycle. Several hypothesis explain the variation in rate of psychiatric problems in poorer individuals as compared to their richer counterparts. According to social selection hypothesis (6), persons with mental illnesses tend to drift down in socio-economic positions and hence are concentrated in the inner cities or the lower strata of the society. On the contrast, social causation hypothesis (7) attributes socio-economic deprivation as an important contributing factor leading to mental illnesses.

As per the World Health Report 2001, there are 450 million people across the world suffering from mental and neurological disorders. Every year one million people commit suicide, and 10-20 million attempt to take their lives. Despite the anticipated rise in such problems, about 40% of countries have no mental-health policy. Two-thirds of the countries spend 1% or less of their health budget on mental health, and half have only one psychiatrist per 100,000 people (8). In the low income countries, high rates of common mental disorders have often been associated with factors such as discrimination, unemployment and living in a period characterized by rapid and unpredictable social changes (9).

Economic Disparities across the World

The gulf between the poor and the rich of the world is widening (10). The

gap in per capita income between the industrialized and developing world is rapidly increasing. Developing countries, with 80% of the world's population, control only 21% of the global gross national product (GNP). Differences in economic and health status within countries are also as great as or greater than those between countries. A 1990 study from the US reported life expectancy of black men aged 15-44 living in the central health district of Harlem in New York as lower than that of a male Bangladeshi of the same age (11).

A number of stressful social conditions are related to poverty and economic disparity, which can affect the mental health. Some of these include unemployment, illiteracy, homelessness, gender discrimination, increased stresses of daily living, poor housing, over crowding, scarcity of food, clothing and shelter, and lack of resources for medical help (12).

Poverty and Mental Health

Two-levels of researches have been conducted to understand the association between poverty and mental illnesses- individual level and area level. Individual-level researches have consistently demonstrated that poverty is significantly associated with high levels of common mental health disorders such as anxiety and depression (13, 14). Area-level analysis have found that in poorer areas, there are high rates of hospital admissions, higher out-patient mental health services and suicide (15). New Haven Study, one of the earliest landmark studies and its follow-up indicated a direct relationship between poverty and high rates of emotional and mental problems. The study also showed that the different social classes accessed different types of treatment facilities (16).

In 1995, the Office of Population Censuses and Surveys in USA in a study on prevalence of psychiatric disorders, reported that unemployment significantly increased the odds of having a psychiatric disorder, with the highest being for alcohol and drug-use disorders, followed by phobia, psychosis, depression and anxiety disorders (17). In another US study of inner city mothers, self-reported poor financial status predicted depressive symptoms independent of socio-economic status, ethnic group and marital status (18).

Two large scale population based studies from Netherlands (19) and Ethiopia (20) found association between unemployment, education and under-achievement, and mood disorders. Unemployment has also been found to be one of the strongest predictors of suicide after adjusting for other socio-economic variables (21).

Studies from the developing countries have also shown a strong association between indicators of poverty especially low education levels and common mental disorders (9). Disparity in educational attainment could be one of the most important factors perpetuating social inequalities in psychiatric disorder in the world. Poor education and low income have been found to be independently associated with increased prevalence of common mental disorders in Northeast Brazil (22). Similar results were reported in a meta-analysis that tried to understand the relationship between socio-economic position and depression (23).

The relationship between deprivation and mental health needs appears to be linear. A prospective study involving 7726 adults, aged 16-75, found a relationship between financial strain at baseline and the onset as well as maintenance of common mental disorders. The relationship stood strong even after adjusting for objective indices of standards of living (24). Relationship to sudden financial loss and suicide, and extreme poverty and suicide is frequently reported in the media where many cases of suicide and extended suicide were cited.

Poverty, Female Gender and Common Mental Disorders

Poverty and female gender have been found to be associated with depression and anxiety in developed as well as in developing countries. In low and middle income countries, women bear the brunt of adversities associated with poverty including less access to education, emotional and physical abuse, sexual trafficking, unwanted pregnancies and fewer job opportunities, hence increasing their vulnerabilities for mental disorders (9). Research has consistently reported presence of depressive symptoms in mothers with low income (25). The development agencies who focus on women as a priority group have failed to recognize their unique vulnerability to common mental disorders and need to reorient their priorities accordingly.

A multinational study conducted in four developing countries, viz. India,

Zimbabwe, Chile and Brazil studied association of common mental disorders with economic deprivation and education. Female gender, low education and poverty were found to be strongly associated with common mental disorders. The study suggested population based prevention strategies based on increasing the proportion of those who complete schooling and acting on high-risk groups such as providing loan facilities to the impoverished (26).

Economic Disparity and Children

Low income accompanied by disruptive environment and poor external support has been found to put children at risk to develop a variety of psychiatric disorders (10). Problems in socially disadvantaged children can be grouped under medical illnesses, emotional and social problems, environmental deprivation, learning disabilities and mental retardation. Psychiatric disorders are a result of interplay between genetic and environmental factors including adverse life experiences. Reviews by World Health Organization have reported that approximately one in five children or adolescents suffer from mental health problems (27).

Poor children not only suffer worse health status and injuries, but also have less access to routine medical care (28, 29). Moreover, they are found to have higher rates of psychiatric disorders and associated impairments like poor school performance, ill-health, tobacco use, and social impairments (30, 31). The harmful effects of poverty on children are more pronounced in the preschool period than at later stages. Almost half of all lifetime cases of mental illnesses begin by age 14. Therefore, early childhood is an important period to predict later economic and health positions.

Poverty and social disadvantage are also strongly correlated with deficits in children's cognitive skills and educational achievements. The number of years that a family lives in poverty has been reported to be associated with negative outcomes in children, even for variables like IQ scores (32). Threatening and erratic discipline, lack of supervision and poor parent-child attachment are known to mediate the effects of poverty especially in development of behavioral disorders such as delinquency and substance use disorders (33).

Social Class and Mental Illness

Relationship between social class and mental illness is one of the earliest and the most firmly established association in psychiatric epidemiology (7). Socially disadvantaged people have higher rates of psychiatric disorders than their advantaged counterparts as measured by treatment statistics, non-specific distress in the community and epidemiological surveys of psychiatric disorders (34). Persons belonging to lower economic positions also have a significantly higher probability of hospitalization and remaining hospitalized longer than their middle class counterparts.

Until the early 1970s, it was thought that the people belonging to lower classes were exposed to more stressful life experiences than those of more advantaged social status, and this differential exposure accounted for the negative relationship between social class and mental illness. However, subsequent work has proven the hypothesis that class-linked vulnerability to stress accounts for the major part of the association between social class and depression, and between social class and non-specific stress (2, 13).

Differential vulnerability may arise in different ways. One is that some type of selection or "drift" of incompetent copers to the lower class might lead to the relationship between class and vulnerability, for example, in cases of psychosis and substance use disorders. The other is that one's experience as a member of a particular class leads to the development of individual differences in coping capacity as well as differences in coping resources, which may be true in cases of anxiety and depression.

Some of the risk factors that make the lower socio-economic group more vulnerable to psychiatric disorders include poor coping styles, ongoing life events, exposure to stress and weak social support system (35). Among various psychiatric disorders, depression is found to have a controversial association with social class. A review found that although lower social class had higher prevalence of psychopathology, the results for depression were more ambiguous with only five studies out of eleven showed higher prevalence of depression in lower social class (36). A recent meta-analysis indicated a strong to moderate correlation between social class and depression with lower socio-

economic status increasing the risk of onset of episode as well as persistence of symptoms (37). Persons belonging to lower social strata are disadvantaged in their access to supportive relationships. There is also evidence that the personality characteristics associated with vulnerability to stress, such as low self-esteem, fatalism, and intellectual inflexibility are more common in lower class people.

The course of illness is also determined by socio-economic status. This may be a result of service related variables like barriers to access to provided services. Poor countries have fewer resources. Even in rich countries, poverty and associated factors like low education, unemployment, racial, ethnic and language minority can create insurmountable barriers to care (8). It has also been found that outcome of mental illnesses is unequally distributed according to social class, with the lower class facing more disabilities and poorer prognosis (38, 39).

Early onset psychiatric disorders are powerful predictors of a wide range of adverse social consequences like school failure, teen childbearing, early marriage, mental instability, job instability and financial adversity. Psychiatric disorders are associated with functional impairments both within the family and work roles. Persons with a history of psychiatric disorders miss more days of work and have lower productivity while at work than the workers in the same job who never had a psychiatric disorder (40). Thus the psychiatric disorders, if not attended well, have a great potential at drifting the socio-economic status of persons with mental illness and further increasing the economic disparities.

Solutions

Interventions need to be undertaken at the policy level and the State needs to take strong initiatives at improving the education and health status of the society and minimize unemployment. Policies of higher taxation of the rich and minimal of the lower income groups, which is often the norm, is also a step towards this direction (41).

The World Bank Group (42) has given certain guidelines to fight poverty, which include improving the distribution of income and wealth, accelerating social development by creating and enhancing education opportunities of girls and women, provision of safe water and sanitation, and immunization of children.

The society has to work towards reducing the inequalities in income by increasing education, employment, housing and healthcare opportunities of its underprivileged population.

Conclusion

Growing economic disparity has close inverse association with mental health. The diversities exist both across the developed and developing countries and within different countries. There is a need to reduce this ever expending gap and to provide adequate cost-effective services to the underprivileged sections of the society.

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Quality of Life and Blood Counts in Cancer Patients Undergoing Chemotherapy - A Cross Sectional Study

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ABSTRACT

Aim: This study evaluates the assessment of Quality of Life (QoL) in cancer patients undergoing chemotherapy using widely accepted European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core-30 (QLQ-C30) and European QoL-5-Dimension 5-Level (EQ-5D-5L) questionnaires.

Purpose of the study: Cancer chemotherapy is associated with several co-morbid illnesses as well as side effects which ultimately affects the QoL of cancer patients. Blood count patterns are adversely affected in cancer patients undergoing chemotherapy. This condition is associated with symptoms like fatigue, dizziness, weakness, etc which in turn affects the quality of life of cancer patient. The present study evaluates the assessment of QoL in cancer patients undergoing chemotherapy using the EORTC QLQ-C30 and EQ-5D-5L questionnaires.

Study design: Prospective, cross sectional, observational study.

Results: The scores of EORTC QLQ C-30 show that there are no significant changes in the QoL scores with the exception of fatigue (i.e., patients reported statistically significant increased levels of fatigue before and after treatment) and pain (statistically

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significant results). No significant results were observed in the scores of EQ-5D-5L questionnaire. There has been a significant change in the blood counts especially neutrophils, platelets and haemoglobin before and after 1st cycle of chemotherapy and during the subsequent cycles there is no significant change.

Conclusions: QoL has become an important endpoint in clinical research on cancer treatment. Even though perception of QoL varies from individual to individual but still it is an important criterion for measurement of the severity of disease and its treatment.

Keywords: Cancer, quality of life, chemotherapy.

Introduction

Cancer is a leading cause of death worldwide and it is the second most common disease in India responsible for maximum mortality with about 0.3 million deaths per year. This is owing to the poor availability of preventive, diagnostic and treatment modalities for the disease. Around 30% of death associated with cancer are due to the five leading behavioral and dietary risks: high body mass index, low fruit and vegetable intake, lack of physical activity, tobacco and alcohol usage (1). Although there are several modalities for cancer treatment, like chemotherapy, radiation therapy, immunotherapy and biologic therapy, are available but the most commonly used modality for cancer is chemotherapy. This treatment modality is employed to attenuate the cancer cell load as well as to improve the patient's Quality of Life (QoL) was found to be associated with several side effects. Chemotherapeutic regimens carry with them an entire spectrum of side effects like anaemia, nausea, vomiting, fatigue, anxiety, loss of appetite, cognitive impairment, alopecia, depression, chemotherapy-related amenorrhea and menopause in females and oligozoospermia, etc. in males. These side effects often affect patient's QoL (2).

Evaluation of QoL has been important nowadays especially for chronic diseases like cancer because it is considered to be indicative of health care quality (3). QoL is a multidimensional and

subjective perception of the positive and negative aspects of cancer symptoms including physical, emotional, social and cognitive function and importantly, disease symptoms and side effects (4). There is as such no gold standard for measuring the QoL; however, researchers have designed certain tools to measure it as accurately as possible. One of such widely used questionnaire is European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core-30 (QLQ-C30) collectively called EORTC QLQ C-30, which is used to assess the QoL in cancer patients. This questionnaire has been validated in several languages (5). It has been used to assess the QoL in different types of cancers like breast, colorectal, lung and ovarian cancer (6-14). EQ-5D-5L, i.e. European QoL-5-Dimension 5-Level Questionnaire is one of the latest questionnaires measuring the QoL in patients with bladder, prostate and breast cancer (15-18).

Since chemotherapy acts by suppressing fast dividing cells like cancer cells, the physiologically fast dividing cells of the bone marrow that are responsible for the first line of immune defense such as neutrophils and other white cells, are also not spared and can also be negatively affected which thereby cause neutropenia or thrombocytopenia in cancer patients undergoing chemotherapy and can in turn affect the QoL adversely (19-22). The aim of the present study was to evaluate QoL in cancer patients at different cycles of chemotherapy and to find its association with blood counts.

Materials and Methods

This prospective cross-sectional study was performed at the HAH Centenary Hospital, Hamdard University, New Delhi, which provides outpatient treatment to cancer patients using the modality of anticancer chemotherapy. Thirty patients of both the genders were enrolled in the study. All the patients were screened and recruited on the basis of pre-defined Inclusion/Exclusion Criteria. Written Informed Consent was obtained from eligible patients willing to participate in the study. The study protocol was approved by Jamia Hamdard Institutional Review Board.

We included patients who : 1) had histologically confirmed cancer; 2) were receiving chemotherapy for the

treatment of cancer; 3) were capable of giving informed consent; 4) were of 18 years and above; 5) can understand and fill out QoL questionnaires, and agree to provide information to be included.

We excluded patients who : 1) had serious, unstable medical or mental illness; 2) had medical contraindication to any study procedure; 3) had been suffering from alcohol or other substance use disorders (esp. cannabis and opioids); 4) have not read and signed informed consent, or do not understand its contents; 5) had psychological, familial, sociological, or geographical conditions that do not permit treatment or medical follow-up and /or prohibit compliance with the study protocol.

EORTC QLQ-C30 is one of the widely used instruments in various cancer populations to measure their QoL. This has been translated and validated in 81 languages and is used in more than 3,000 studies worldwide. It consists of 30 items rated on a 1 to 4 scale (two questions are rated between 1 and 7). The items comprise of 15 domains many of which address physical symptoms: general health status, physical functioning, emotional functioning, cognitive functioning, social functioning, fatigue, nausea/ vomiting, pain, dyspnea, insomnia, lack of appetite, constipation, diarrhea and financial problems. The EuroQol EQ-5D-5L is a generic preference-based measure of health-related QoL. It is a standardized non-disease-specific (generic) instrument for assessing self-reported health status, allowing for comparisons across disease groups. The EQ-5D-5L consists of a general health descriptive system-based on five dimensions and a 100-point visual analogue scale (VAS). The dimensions cover mobility, self care, usual activities, pain/discomfort, and anxiety/depression and are characterized by five levels. The patients answered both the questionnaires initially at baseline and then after each cycle of chemotherapy. Blood counts were assessed using blood test reports before and after each cycle of chemotherapy.

Results

Baseline characteristics of patients enrolled

Thirty patients were chosen on the basis of inclusion and exclusion criteria. These patients followed-up upto at least one

cycle of chemotherapy. The mean ages (in year) of the patients were 51.16±9.35. Out of the 30 patients 50% were male and 50% were female. The most common type of cancer observed in these patients was gastrointestinal (30%) followed by breast cancer (23.33%) and then oral cancer (20%). The most widely used chemotherapeutic regimen given to such patients included Paclitaxel/Docetaxel, Cisplatin/Carboplatin (accounting for about 33.33%) and 5 FU, Cisplatin/ Carboplatin (accounting for about 13.33%). Most of the patients in the study who were enrolled had completed their I cycle (about 46.66%) (Table 1).

Changes in QoL over a cycle of chemotherapy

An overall change in aspects of QoL before and after a cycle of chemotherapy using the EORTC QLQ C-30 questionnaire was observed. The scores of EORTC QLQ C-30 included both the global QoL and the symptom scale. There was no significant change in the QoL scale with the exception of fatigue (i.e., patients reported statistically significant increased levels of fatigue before and after treatment) and pain (patients reported statistically significant pain) (Table 2). There was an overall change in aspects of QoL before and after a cycle of chemotherapy using an EQ-5D-5L questionnaire. The scores included five broad domains (mobility, self care, usual activities, pain and anxiety/depression). No significant changes were observed in this questionnaire scores (Table 3). There was no significant change observed in QoL items according to sex, except for pain which was significant in both males and females (Table 4). Although there have been changes in the mean cognitive functioning in patients of age above 56 years from 77.27 to 66.67 but the change is not significant. For patients above 56 years, significant changes have occurred in the physical functioning and fatigue (Table 5).

Changes in blood counts over a cycle of chemotherapy

As per Table 6, there has been a significant change in the blood counts especially neutrophils, platelets and haemoglobin before and after 1st cycle of chemotherapy. There is no significant change in the subsequent cycles.

Table 1. Baseline characteristics of patients enrolled

Characteristic	Categories	Number (%)
Age	Mean	51.16
	S.D	9.35
Gender	Male	15(50)
	Female	15(50)
Type of Cancer	Gastrointestinal	9(30)
	Breast	7(23.33)
	Neck	1(3.33)
	Oral	6(20)
	Sarcoma	1(3.33)
	Non Hodgkin lymphoma	2(6.66)
	Ovary	1(3.33)
	Lung	2(6.66)
	Brain	1(3.33)
Chemotherapeutic Regimen	FOLFOX(5 FU, Leucovorin Calcium Oxaplatin)	4(13.33)
	5 FU, Cisplatin/Carboplatin	6(20)
	Adriamcycin, Cyclophosphamide	3(10)
	Rituximab/Transtuzumab	4(13.33)
	Gemcitabine,Cisplatin	3(10)
	Paclitaxel/Docetaxel, Cisplatin/Carboplatin	10(33.33)
Cycle of Chemotherapy	1	14(46.66)
	2	4(13.33)
	3	4(13.33)
	≥4	8(26.66)
Patient demographics expressed as Number and Percentage		

Table 2: Changes in QoL score of EORTC QLQ C-30 over a cycle of chemotherapy

Questionnaire	Before Chemo-therapy (SEM)	After Chemo-therapy (SEM)	Mean difference	p-value
Global QoL	80±52.5	75.00±46.68	5.000	0.573
Physical Functioning	67.33±26.34	63.33 ± 13.98	4.000	0.323
Role Functioning	63.33 ± 39.97	75.56 ± 23.46	-12.222	0.108
Emotional Functioning	57.78± 33.90	51.94 ±30.30	5.833	0.272
Cognitive Functioning	67.22 ± 32.01	70.00 ± 26.77	-2.778	0.538
Social Functioning	80.00 ± 27.47	75.00 ±29.28	5.000	0.248
Symptom Scale				
Fatigue	47.41 ± 32.22	73.70 ± 27.136	-26.296	0.003
Nausea and Vomiting	30.00 ± 32.28	19.44 ± 22.78	10.556	0.149
Pain	47.78 ± 33.83	37.78 ± 21.41	10.000	0.080
Dyspnoea	14.44 ± 25.80	6.67 ±16.14	7.778	0.090
Insomnia	40.00 ± 41.43	41.11± 36.81	-1.111	0.845
Appetite Loss	43.33 ± 39.29	43.33±38.31	0.00	1.00
Constipation	33.33 ± 41.06	36.67± 36.46	-3.333	0.698
Diarrhoea	13.33± 29.81	10.00 ± 27.89	3.333	0.476
Financial Difficulties	45.56± 38.64	52.22 ± 39.81	-6.667	0.312
Results expressed as Mean ± S.D p- value < 0.05 considered as significant				

Table 3: Changes in Qol scores in EQ-5D-5L over a cycle of chemotherapy

Questionnaire	Before Chemo-therapy (SEM)	After Chemo-therapy (SEM)	Mean difference	p-value
Mobility	1.87 ±1.07	2.03 ± 1.03	-0.167	0.344
Self Care	1.57 ± 0.90	1.53 ± 0.63	0.033	0.845
Usual Activities	2.03 ± 1.22	2.07 ± 1.05	-0.033	0.891
Pain/Discomfort	2.07 ± 1.17	1.83 ± 0.99	0.233	0.199
Anxiety/Depression	2.00 ± 1.20	1.97 ± 0.96	0.033	0.865
Visual Analogue Scale	56.17 ± 23.73	55.50 ±20.69	0.667	0.865
Results expressed as Mean ± S.D p- value < 0.05 considered as significant				

Association of blood count parameters and QoL

Changes in the blood counts adversely affect the QoL. The results show that there was a significant correlation between nausea and vomiting and neutrophil count. The results also demonstrate that there is no significant correlation between platelet and QoL parameters but there was a significant correlation between haemoglobin and social functioning as well as cognitive functioning (Table 7).

Discussion

An important issue in cancer care and research is QoL. The QoL refers to 'global wellbeing' including physical, emotional, mental, social and behavioral components. In the recent past, a number of QoL tools have become available to measure health-related QoL. The most widely used applicable instrument to measure the QoL in cancer patients is EORTC QLQ C-30. EQ-5D-5L has been the latest questionnaire used to measure QoL in cancer patients. The present study assessed the QoL in cancer patients

Table 4: Changes in Qol scores in EORTC QLQ C30 over a cycle of chemotherapy according to sex

Questionnaire	Before Chemotherapy (SEM)	After Chemotherapy (SEM)	Mean difference	p-value	Before Chemotherapy (SEM)	After Chemotherapy (SEM)	Mean Difference	p-value
EORTC QLQ C30	Males				Females			
Global QoL	92.22 ±62	71.11±57.55	21.111	0.189	67.78±38.04	78.89±34.20	0.889	0.126
Physical Functioning	69.78±29.69	62.67±13.52	7.111	0.282	64.89±23.29	64.00±14.86	-10.000	0.858
Role Functioning	64.44± 42.2	78.89±27.07	14.444	0.246	62.22±39.07	72.22±19.59	0.556	0.287
Emotional Functioning	63.89±33.28	52.78±27.03	11.111	0.248	51.67±34.53	51.11±34.20	0.556	0.910
Cognitive Functioning	77.78±29.32	84.44±11.73	-6.667	0.334	56.67±32.00	55.56±29.99	1.111	0.855
Social Functioning	86.67±24.56	85.56±23.46	1.111	0.865	73.33±29.41	64.44±31.41	8.889	0.135
Symptom Scale								
Fatigue	60.00±31.37	73.33±21.33	13.333	0.147	68.89±32.58	62.96±28.69	5.926	0.488
Nausea and Vomiting	27.78±34.88	20.00±21.08	7.778	0.517	32.22±30.52	18.89±25.09	13.333	0.138
Pain	44.44±33.73	44.44±24.12	0.000*	1.000	51.11±34.77	31.11±16.51	20.000	0.012*
Dyspnoea	13.33±27.60	11.11±20.57	2.222	0.719	15.56±24.77	2.22±8.61	13.333	.054
Insomnia	35.56±40.76	40.00±33.81	-4.444	0.634	44.44±43.03	42.22±40.76	2.222	0.751
Appetite loss	44.44±37.09	42.22±34.43	2.222	0.818	42.22±42.66	44.44±43.03	-2.222	0.843
Constipation	26.67±36.08	42.22±38.76	15.556	0.150	40.00±45.77	31.11±34.43	8.889	0.512
Diarrhoea	13.33±30.34	6.67±18.69	6.667	0.458	13.33±30.34	13.33±35.19	0.000	1.000
Financial difficulties	44.44±39.17	46.67±41.40	-2.222	0.806	46.67±39.44	57.78±38.76	-11.111	0.265
Results expressed as Mean ± S.D, p- value < 0.05 considered as significant								

Table 5: Changes in QoL according to Age

	Global QoL			Physical Functioning			Role Functioning		
Age	**Before Chemo-therapy**	**After Chemo-therapy**	**p-value**	**Before Chemo-therapy**	**After Chemo-therapy**	**p-value**	**Before Chemo-therapy**	**After Chemo-therapy**	**p-value**
25-35	88.89±49.92	87.50±29.41	0.908	64.44±32.82	63.33±18.96	0.894	66.67±35.53	83.33±21.32	0.097
46-55	61.90±52.45	69.05±51.31	0.802	59.05±29.17	63.81±14.33	0.550	71.43±36.91	78.57±12.60	0.689
Above 56 years	81.82±56.00	65.15±58.90	0.184	75.76±13.42	63.03±6.90	0.003*	54.55±47.78	65.15±28.34	0.485
	Emotional Functioning			**Cognitive Functioning**			**Social Functioning**		
25-35	60.42±34.29	60.42±31.81	1.00	63.89±73.61	73.61±31.35	0.067	86.11±29.16	81.94±30.53	0.191
46-55	55.95±33.23	58.33±25.46	0.863	57.14±33.13	69.05±17.82	0.394	80.95±26.23	78.57±31.50	0.859
Above 56 years	56.06±36.91	38.64±29.17	0.126	77.27±25.03	66.67±27.89	0.111	72.73±27.15	65.15±26.30	0.378
Symptm Scale	**Fatigue**			**Nausea and Vomiting**			**Pain**		
25-35	59.26±34.27	58.33±24.22	0.926	19.44±22.29	9.72±16.60	0.206	47.22±39.46	29.17±25.75	0.053
46-55	61.90±35.53	61.90±27.11	1.00	38.10±41.63	19.05±22.42	0.364	54.76±31.50	42.86±21.21	0.283
Above 56 years	25±11.50	98.61±3.92	0.00*	36.36±34.82	30.30±25.62	0.668	43.94±30.98	43.94±13.48	1.00
	Dyspnoea			**Insomnia**			**Appetite loss**		
25-35	8.33±15.08	5.56±19.25	0.586	30.56±41.34	27.78±39.78	0.723	38.89±39.78	52.78±50.17	0.210
46-55	4.76±12.60	00.00±00.00	0.356	28.57±29.99	47.62±37.80	0.231	47.62±46.58	38.10±35.63	0.631
Above 56 years	27.17±35.96	12.12±16.82	0.176	57.58±44.95	51.52±31.14	0.506	45.45±37.34	36.36±23.35	0.506
	Constipation			**Diarrhoea**			**Financial Difficulties**		
25-35	47.22±48.11	27.78±39.78	0.152	2.78±9.62	0.00±0.00	0.339	36.11±41.34	38.89±42.24	0.754
46-55	28.57±35.63	52.38±42.41	0.253	23.81±41.79	0.00±0.00	0.182	28.57±29.99	42.86±46.00	0.510
Above 56 years	21.21±34.23	36.36±27.71	0.242	18.18±34.52	36.36±27.71	0.082	66.67±33.33	72.73±25.03	0.506

Results expressed as Mean ± S.D
P value < 0.05 considered as significant

Table 6: Changes in blood counts according to cycle of chemotherapy

Blood Counts	Before Chemo-therapy (SEM)	After Chemo-therapy (SEM)	Mean difference	p-value
1st cycle				
Neutrophils	69±17	57±17	13	0.0006*
Platelets	2.47 ± 0.786	2.19±1.02	0.28	0.0241*
Haemoglobin	12.57±1.54	10.92±1.15	1.65	0.000431*
2nd Cycle				
Neutrophils	63±7	56±20	6	0.201185
Platelets	2.62±0.55	2.67±0.74	0.05	0.392606
Haemoglobin	12±1.63	11.65±1.65	0.35	0.16843
≥ 3 Cycle				
Neutrophils	61±0.15	64±0.11	3	0.213759
Platelets	2.63±1.13	2.57±1.02	0.06	0.205854
Haemoglobin	11.64±1.71	11.40±1.55	0.24	0.08715
Results expressed as Mean ± S.D p- value < 0.05 considered as significant, p- value = 0.000 is highly significant				

Table 7: Correlation between Neutrophils, platelet count and haemoglobin with Quality of Life parameters after chemotherapy

Quality of Life Parameters	Neutrophils Counts		Platelet Counts		Haemoglobin Count	
	Pearson Correlation	P-value	Pearson Correlation	P-value	Pearson Correlation	P-value
Physical Functioning	0.015	0.938	-0.309	0.097	-0.069	0.717
Role Functioning	0.186	0.326	-0.019	0.922	0.242	0.198
Emotional Functioning	0.116	0.543	-0.191	0.311	0.117	0.539
Cognitive Functioning	0.139	0.463	-0.207	0.272	0.399	0.029*
Social Functioning	-0.009	0.962	-0.116	0.543	0.393	0.032*
Fatigue	-0.077	0.685	0.095	0.618	0.015	0.939

Nausea and Vomiting	-0.437	0.016*	0.083	0.663	-0.044	0.818
Pain	0.051	0.788	-0.126	0.508	-0.200	0.289
Dyspnoea	0.048	0.802	0.143	0.452	0.177	0.351
Insomnia	0.008	0.965	0.087	0.648	-0.155	0.413
Appetite Loss	-0.136	0.473	0.135	0.475	0.167	0.377
Constipation	0.013	0.944	-0.012	0.951	0.013	0.947
Diarrhoea	-0.101	0.594	-0.117	0.540	0.011	0.956
Financial Difficulties	0.154	0.418	-0.093	0.626	-0.174	0.357
Global Health Status/QoL	0.110	0.564	0.195	0.302	0.090	0.635

using both EORTC QLQ C-30 and EQ-5D-5L questionnaires in cancer patients undergoing anticancer chemotherapy.

The present study is a prospective cross-sectional study designed to investigate the QoL in patients suffering from cancer and receiving chemotherapy using validated EORTC QLQ C-30 and EQ-5D-5L and also to find the association between blood count parameters and QoL. Furthermore this study also aimed at evaluation of changes in different parameters such as physical role, cognition, emotional, social, fatigue, pain, nausea/vomiting, dyspnoea, insomnia, loss of appetite, constipation, diarrhea and financial problems in accordance with gender, age, cycle of chemotherapy, different stages of cancer and different chemotherapeutic regimen.

In this study, majority of QoL parameters in the EORTC QLQ C-30 did not change considerably over a cycle of chemotherapy with the exception of fatigue which is in agreement with literature (23). There are no changes in QoL scores according to age and gender, in our study which is similar to previous studies.

There was not much change in the parameters of QoL as measured by scores obtained by EQ-5D-5L questionnaire. According to the VAS of the EQ-5D-5L, there was no significant improvement over the cycle of chemotherapy. This observation is inconsistent with the conclusion drawn in an earlier study (17), where a significant improvement in VAS scores was observed.

Chemotherapeutic regimen used in this study (Platinum compounds and taxanes) have been reported in previous studies to lower the QoL of cancer patients (18). These two classes of agents carry with them entire spectrum of side effects that often significantly affect a patient's QoL. Patients, who received first-line carboplatin-based chemotherapy reported to possess a higher global QoL and fewer symptoms of nausea and vomiting, appetite loss and constipation in comparison to those who received cisplatin-based chemotherapy. Outcomes of majority of studies showed fewer symptoms of nausea and vomiting from carboplatin-based chemotherapy. In the present study, difference in QoL due to nausea and vomiting among the various age groups was found to be statistically insignificant due to small sample size of the study population.

Fatigue is "a persistent, subjective sense of tiredness-related to cancer or cancer treatment that interferes with the usual functioning" (24, 25). It is one of the most common symptom found in all patients irrespective of stage of cancer, type of cancer and chemotherapeutic regimen. It has been found in our study as well. Consistent with previous studies (24, 26) fatigue and pain was largely associated with HRQoL. The symptom distress including increased severity of nausea at the time of treatment and at midpoints of chemotherapy cycle has been noted to intensify fatigue level. It has been reported that during cancer chemotherapy treatments, fatigue level was moderately intense, compromising HRQoL levels. It has been found that fatigue increases with age in patients. This has been found in our study as well. Patients above 56 years had a statistically significant change in fatigue scores. The reason for such change may be natural changes, co-morbidities associated with ageing, etc. Some factors identified as contributing factors to cancer fatigue include immobility, de-conditioning, sleep disorders, use of centrally acting drugs, anaemia and decline in functional reserve of organ systems.

Blood counts are measured throughout the cycles of chemotherapy. It is a pre-requisite investigation done on all cancer patients before surgery, use of chemotherapy and/or radiotherapy. The most common blood count parameters adversely affected by chemotherapy were platelets, neutrophils and haemoglobin (20). In our study we have found that

there was a statistically significant change in the blood counts especially haemoglobin, neutrophils and platelets before and after a cycle of chemotherapy. Changes in blood counts can be correlated to change in QoL parameters. Changes in haemoglobin levels cause anaemia leading to deleterious effect on QoL (19, 26). In the present study, a positive correlation between the social and cognitive functioning and haemoglobin levels has been found. Even though fatigue has been strongly correlated with anaemia in other studies (17, 19), but this was not evident in our study. Anaemia is the single most powerful independent determinant of fatigue. It may develop as a result of the malignant disease process itself; from bleeding, nutritional deficiencies, bone marrow damage, tumour infiltration of the bone marrow, or immunologic impairment of the haematopoietic response (27).

Neutropenia is a common toxicity in patients undergoing anticancer chemotherapy. Most cancer chemotherapies work by suppressing fast dividing cancer cells, however, the physiologically fast dividing cells of the bone marrow, which are responsible for producing the cells involved in the first line immune defense such as neutrophils and other white cells may also get affected (22). Hence, an impaired immune system leads to a poor QoL. In our study, neutrophil count has been positively correlated with QoL parameters.

Conclusion

The results of this study have important implications in both clinical and research practice. It suggests that QoL should be considered while prescribing anticancer chemotherapeutic interventions to patients. Regular QoL assessment should be done throughout the course of treatment. QoL monitoring coupled with treatment to improve appetite loss, global health and function scale may enhance the quality survival of the patients. Blood counts should also be monitored throughout the treatment and proper need-based palliative care should be provided to patients.

The study had certain limitations. Firstly, the small sample size which could be one of the important reasons of not finding statistically significant associations among demographical variables such as age, gender, type of cancer and anticancer chemotherapeutic regimens. Another limitation was that we took patients from different treatment

cycles which vary in relation to different variables and that cannot be commented upon with surety. It could be informative to prospectively follow-up these patients in order to assess the time course of the symptoms and outcomes.

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