



ORIGINAL RESEARCH PAPER

Oncology

A CLINICAL STUDY OF ORAL MANIFESTATIONS IN CANCER PATIENTS ON CHEMOTHERAPY

KEY WORDS: chemotherapy, oral mucositis, quality of life

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ABSTRACT

Background: There has been an increase in the cancer related morbidities; a significant part of it being related to the therapies. The chemotherapeutic side effects are due to low-specificity of drugs, there by cells of high metabolic rate including oral cavity, skin and its appendages, epithelium of the gastrointestinal tract, and bone marrow are frequently affected.
Aim: To determine the frequency and significance of oral manifestations in patients on anticancer chemotherapy
Methods: A total of 50 patients attending the oncology outpatient department or those admitted in the oncology ward Yenepoya Medical College Hospital, Mangalore between June 2017 and August 2017, hair loss related to chemotherapy were noted.
Results: Oral changes were mainly in the form of mucositis in 48%, the most common subjective symptoms among them were metallic taste and soreness/burning sensation seen in 45% and 26% respectively.
Conclusion: Although according to the literature oral health status of cancer patients is similar to that of general population, oral complications due to chemotherapy would not only hinder the recovery of general health in cancer patients but affects the quality of life

Introduction

Cancer is one of the principal causes of death in both developing countries and developed. Cases in developing countries account for 57% of new cases and 65% of cancer deaths worldwide.¹ The effectiveness of cancer treatment has continued to improve over the past decades with contemporary cancer treatment modalities including chemotherapy, radiotherapy, surgical resection and hematopoietic stem cell transplantation (HSCT). Among these modalities Radio- and chemotherapy can cause direct harm to the soft and hard tissue of the oral structures.²

Chemotherapeutic agents are widely used in every step of cancer therapy as a primary agent or as neoadjuvant or adjuvant in preoperative, postoperative or as a separate treatment of certain types of cancers.³

It is important to note that chemotherapy causes possible complications along with the many therapeutic benefits which is due to low specificity of the drugs.³ Due to their high metabolic rate chemotherapy targets rapidly growing structures like mucocutaneous tissues, hair follicles and nail matrix. Hence a significant number of adverse effects are related to the oral cavity, skin and its appendages.⁴

The main inconvenience of chemotherapy is its lack of selectivity, since it acts upon both tumor cells and rapidly multiplying normal cells. The oral cavity is lined with rapidly dividing keratinising or non-keratinising stratified squamous epithelium.

Chemotherapy also modifies the bacterial flora in the oral cavity and reduces the salivary secretion which further leads to failure of mucosal regeneration.³

Oral complications are seen in about 40% of the patients taking chemotherapy. These complications are often associated with drugs that affect the synthesis of DNA.⁵

Oral mucositis is the main dose-limiting reaction of most chemotherapeutic drugs.

The various drugs implicated with oral mucositis are bleomycin, dactinomycin, methotrexate, topotecane, and fluorouracil. The effect could be direct or indirect toxicity by bone marrow suppression.⁵

Hence appropriate treatment and maintaining oral health is essential in the preservation of daily functions, such as eating, verbal and nonverbal communications, and the prevention of

infectious diseases.²

The present study has been undertaken to determine the frequency and significance of oral manifestations in patients on anticancer chemotherapy. Information about the oral manifestations, underlying malignancy and treatment taken will be analyzed.

Aims

To determine the frequency and significance of oral manifestations among patients on anticancer chemotherapy

Materials and methods

It is a prospective observational study conducted over 2 months on 50 patients taking chemotherapy (after 2nd cycle), admitted under Department of Oncology, Yenepoya Medical College Hospital, Mangalore. and 50 age and sex matched controls were included in the study. Detail treatment history, oral signs and symptoms of 124 patients on chemotherapy, admitted oncology ward were collected; patients with significant clinical findings were included in the study. All the cancer patients on chemotherapy with oral manifestations, admitted under the department of Oncology, YMCH who consent to participate in the study were included in the study. Age and sex matched normal individuals are taken as controls. The patients on radiotherapy or adjuvant chemotherapy and those who were not consenting were excluded from the study.

The study was approved by the Institutional Ethics Committee. The nature of the study was explained to the patients, and a written informed consent was obtained from each patient willing to participate in the study.

A specially designed pro forma was used to record the patients demographic data, previous history of oral pathology, presence of comorbid diseases, type of carcinoma, type of chemotherapy and its regimen. A short questionnaire about the quality of life is prepared, where in patients were asked whether they had any difficulty in swallowing food or having spicy food, whether their oral condition hindering their daily activities of life and does it disrupt social activities of life and makes you pessimistic about the future.

All the oral findings were recorded in the proforma. Mucositis was defined as "inflammation or ulceration of the oral mucosa occurring during cancer chemotherapy that cannot be characterized clinically or histologically as any other disease," and was graded according to recommendations by the WHO. The

presence of mucosal pigmentation, whitish plaques, hemorrhagic crusts, erosions in any part of the oral cavity during the chemotherapy were noted. The diagnosis of candidiasis and herpes was based on the clinical, KOH mount and Tzanck smear respectively.

The study was conducted for duration of 3 months after obtaining the ethical clearance. Collection of data and writing up of the literature review were simultaneously done. Compilation of data, statistical analysis and writing of the final manuscripts were done at the end of three months

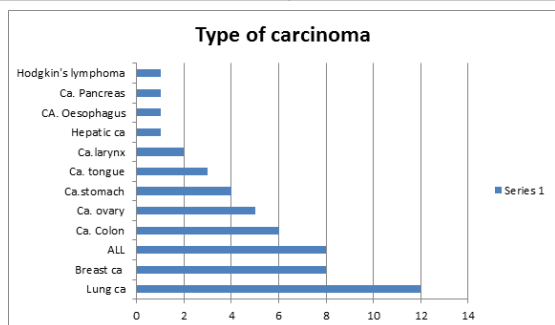
RESULTS

The study group includes 50 cancer patients receiving chemotherapy out of which 16 patients were on a single chemotherapy drug and 34 were on combined chemotherapy.

The various chemotherapy regimens and drugs used in the study were: paclitaxel, vincristine, vinblastine, 6-mercaptopurine, 5-fluorouracil, cytarabine, gemcitabine, cisplatin, carboplatin, cyclophosphamide, doxorubicin, daunorubicin, epirubicin, hydroxyurea, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), and ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) regimens.

Table: 1 Type of carcinoma in study population (n=50)

Type of cancer	No. of patients
Lung cancer	12
Breast cancer	8
ALL	8
Cancer of colon	6
Ovarian cancer	5
Cancer stomach	4
Cancer of tongue	3
Cancer of larynx	2
Hepatic cancer	1
Cancer oesophagus	1
Cancer pancreas	2
Hodgkin's lymphoma	1



In the study Lung cancer was the most common cancer seen in 12 patients followed by breast cancer in 8 patients, acute lymphocytic leukaemia (ALL) in 8 and cancer of colon in 6 patients. The other cancers encountered were ovarian cancer 5, cancer stomach 4, cancer of tongue 3, cancer of larynx 2, hepatic cancer 1, cancer oesophagus 1, cancer pancreas 2, and Hodgkin's lymphoma 1.

In the study severity and frequency of pathological changes occurred in the oral cavity of patients in the control and the study group are depicted in tables 1 and 2. In about 94% of patients from the control group there was no mucositis. In healthy population Candidiasis was seen in one patient, rest of the two with mucositis only had mild erythema with soreness. Mucosal pigmentation is seen in about 6% of healthy population. Inflammatory changes are noted in 6% of healthy subjects only in the form of mild erythema and soreness.

In the study group of patients treated with chemotherapy, 48% of patients had inflammatory changes of the soft tissues, which is significantly higher in intensity than in the healthy group Lesions.

Oral lesions associated with pain occurred in over 28% of patients. Two of the patients were unable to consume solid diet due to the same. Candidiasis was noted in 16% of study population, where as only 2% of control population had candidiasis. Herpes and pigmentation was seen in 2% each of study population. About 6% of control population had pigmentation of oral mucosa which is higher than that of study population. It could be due smoking and poor oral hygiene.

Table 4 Questionnaire on quality of life showed the following results: all patients were willing to take chemotherapy despite the adverse effect of hair loss, 45 (90%) had unpleasant metallic taste, 26(52%) had soreness and burning sensation of mouth, Bleeding gums (gingivitis) were complained by 2(4%) patients, 15(30%) patients had difficulty in talking/ communicating, 8 (16%) patients had difficulty in intake of food.

Table: 2 WHO grading system for mucositis based on clinical appearance and functional status.

Grade	No. Of patients with lesions in study group	Percentage of patients with lesions in study group	No of patients with lesions in control group	Percentage of patients with lesions in study group
0 (none)	26	52%	47	94%
I (mild): Oral soreness, erythema	15	30%	2	4%
II (moderate): Oral Erythema, ulcers, solid diet tolerated	7	14%	1	2%
III (severe): Oral Ulcers, liquid diet only	2	4%		
IV (life-threatening): Oral alimentation impossible	0	0		

Table: 3The incidence of pathological lesions of the mucous membranes

Pathologica l lesions of oral mucosa	Number of patients from study group with lesion	Percentage of patients from study group with lesion	Number of patients from control group with lesion	Percentage of patients from control group with lesion
Candidiasis	8	16%	1	2%
Herpes	1	2%	0	0
Pigmentation	1	2%	3	6%

Table: 4The prevalence of subjective symptoms among examined patients (Questionnaire on quality of life)

Subjective symptoms	Yes (study group)	No(study group)	Yes (control group)	No (control group)
Feeling unpleasant metallic taste	45	5	4	46
Feeling of mouth soreness / burning sensation	26	24	2	48
Bleeding gums (gingivitis)	2	48	0	0
Difficulty in talking/ communicating	8	42	0	0
Difficulty in swallowing of food	15	35	0	0

DISCUSSION

Chemotherapy forms an integral part in the multifaceted approach to the management of cancers.⁶ Both newer chemotherapy agents having specific targets in the pathogenesis of malignancies and older agents are associated with a variety of cutaneous adverse events.⁷ These drugs have a small therapeutic index and thus may be toxic to the rapidly proliferating cells of the skin, hair and nails at therapeutic doses resulting in a wide array of cutaneous side effects.⁶

Global cancer statistics report that cancers affecting the stomach and lung are the most prevalent cancers among males followed by malignancy of oesophagus.⁸ In this study carcinoma affecting the lung (12, 24%) and hematologic system (9, 18%) were the most common cancers among men followed by carcinoma (6, 12%) and carcinoma stomach (4, 8%). Among females the most common cancer was breast cancer (8, 16%) and carcinoma ovary (5, 10%). Kirthi et al reported that among females breast carcinoma (40%), carcinoma cervix (11.4%) and carcinoma ovary (8.6%) were the most commonly encountered cancers and among male patients, lung carcinoma (10%) and urinary bladder (8.3%) were the most frequently observed cancers.⁹

In this study the most commonly prescribed chemotherapeutic drugs were cisplatin (25, 50%) followed by cyclophosphamide (10, 20%), carboplatin (6, 12%), paclitaxel (5, 10%) and 5 fluorouracil (4, 8%). In the study by Kirthi et al the drugs employed for chemotherapy were similar to those in this study with cisplatin being the most commonly prescribed followed by Adriamycin, 5-fluorouracil and cyclophosphamide.⁹

The term oral mucositis was introduced in the late 1980s, refers to inflammation of the oral mucosa induced by radiotherapy (seen in 80% of all patients), chemotherapy (in approximately 40-50%), or bone marrow transplantation (in over 75% of all patients), and is considered a manifestation of Leukopenia.^{10,11}

In the present study 48% of patients had mucositis (inflammatory changes of the soft tissue)

In Rahnama M et al study 58% had oral mucositis.³

Elting et al conducted a study 599 patients over 1236 cycles of chemotherapy where in 37 % had inflammatory changes of mucosa.¹¹

An important and frequently occurring complication of chemotherapy is oral candidiasis. Fungal infections are promoted by reduction of salivation, neutropoenia, lymphocyte disorders, and changes in the bacterial flora of the oral cavity.¹²

In study conducted by Rahnama M et al, 29(50%) patients on chemotherapy had fungal changes.³

In the present study 16% of study population and 2% of normal population had candidiasis In Lalla et al study the prevalence of oral fungal infection in all cancer treatments including chemotherapy and head and neck radiation was about 7.5% before treatment, 40% during treatment.¹³

In the review of 17 studies published by Lalla et al, the prophylactic administration of fluconazole during cancer therapy was seen to reduce the prevalence of clinically manifest fungal infections, including systemic infections, to 1.9%.¹³

Elad et al (2010) study reported that about 50% of patients with haematological malignancies on chemotherapy had HSV infection and none of the patients (0%) receiving radiation therapy for head and neck cancer had HSV. where as in patients receiving combined radiation and chemotherapy the prevalence increased to nearly 40%.¹⁴

The incidence of oral lesions produced by recurrent HSV in cancer patients with bone marrow suppression has decreased considerably following the introduction of prophylactic acyclovir.

10,13

In the present study only 2% of study population had herpes lesions Brown et al., in a study on 223 cases of patients undergoing systemic antitumor therapy reports soreness of the mouth in 51% of these patients which is similar to our study where in 52% of patients in study group and 4% of control group had the symptom.¹⁵

In Hovan et al study 50–75% of cancer patients taking CT, RT or both have disguesia where in our study showed high prevalence, which is 90% of study population.¹⁶

In a study conducted on 88 patients by Cheng undergoing cancer therapy 40% reported difficulties in swallowing which is coherence with the present study where in 30 % of the study population reported difficulty in swallowing food.¹⁷

Due to smoking habits 6% of control population had oral mucosal pigmentation which is less noted in study population (2%)

50 patients satisfying the inclusion and exclusion criteria were included in the study

The age range of patients in our study was 6- 74 years. The maximum number of patients, (56%) was in age group 40-60.

Male preponderance was seen with a male to female ratio of 1.4:1. The most common indications for chemotherapy therapy were carcinoma lung (24%) and carcinoma breast (16%).

The most commonly administered drug was cisplatin (45%) followed by cyclophosphamide (23%), carboplatin (18%), paclitaxel (18%) and 5 fluorouracil (17%).

CONCLUSION

Fifty patients on cancer chemotherapy were included in this study and 24(48%) patients had oral mucositis which was attributable to chemotherapy. An analysis of the data has enabled this study to arrive at the following conclusions:

- Male preponderance was seen with male to female ratio of 1.4:1
- The most common indication for chemotherapy was carcinoma lung followed by carcinoma breast.
- Patients received chemotherapy with a single agent or combination therapy comprising of 2, 3 or 4 drugs.
- Cisplatin, cyclophosphamide, 5 fluorouracil, carboplatin, paclitaxel and doxorubicin were the most frequently prescribed chemotherapeutic drugs.
- Cytotoxic therapy is often associated with the occurrence of side effects in the oral cavity, due to the low specificity of the action of chemotherapeutic agents.

Regular and frequent oral cavity examination is essential in patients receiving chemotherapy when compared to healthy subjects to avoid risk of oral complication Prophylactic anti fungal therapy and anti viral therapy had decreased prevalence of oral candidiasis and oral HSV

Figure : 1 Herpetic gingivitis with mucositis



Figure : 2 Apthous ulcer with mucositis



Figure 3: Hyperpigmentation of mucosa and hard palate**REFERENCES**

1. Parkin D. Global cancer statistics in the year 2000. *The Lancet Oncology*. 2001;2(9):533-543
2. Wong HM. Oral complications and management strategies for patients undergoing cancer therapy. *ScientificWorldJournal* 2014; 2014:581795.
3. Rahnama M, Madej-Czerwinka B, Jastrzębska-Jamrogiewicz I, Jamrogiewicz R. Analysis of the influence of parenteral cancer chemotherapy on the health condition of oral mucosa. *Contemporary Oncology* 2015; 19(1):77-82.
4. Adverse mucocutaneous reactions to chemotherapeutic agents - part I. *An Bras Dermatol* [Internet]. 2016;85(4). Available from: <http://dx.doi.org/10.1590/S0365-05962010000400003>
5. Sanches Junior JA, Brandt HR, Moure ER, Pereira GL, Criado PR. Adverse mucocutaneous reactions to chemotherapeutic agents: part I. *An Bras Dermatol*. 2010 Jul-Aug;85(4):425-37. Review. English, Portuguese. PubMed PMID: 20944902.
6. Hasnat A, Poddar S, Sultana R, Sultana R, Akbor M, Azad M. Pattern of Adverse Drug Reactions Due to Cancer Chemotherapy in Tertiary Care Teaching Hospital in Bangladesh. *Dhaka Univ J Pharm Sci*. 2010;8(1).
7. Susser W, Whitaker-Worth D, Grant-Kels J. Mucocutaneous reactions to chemotherapy. *Journal of the American Academy of Dermatology*. 1999; 40(3):367-398.
8. Fabbrocini G, Izzo R, Panariello L, Monfrecola G. Skin reactions secondary to anticancer agents. *EMJ Dermatol*. 2013; 1:38-43.
9. Kirthi C, Afzal A, Reddy M, Ali SA, Yerramilli A, Sharma S. A study on the adverse effects of anticancer drugs in an oncology center of a tertiary care hospital. *Int J Pharm Pharm Sci* 2014;6:580-3
10. Chaveli López B, Gavalda Esteve C, Sarrion Pérez MG. Dental treatment considerations in the chemotherapy patient. *J Clin Exp Dent*. 2011;3:e31-42.
11. López-Castaño F, Oñate-Sánchez RE, Roldán-Chicano R, Cabreri zo-Merino MC. Measurement of secondary mucositis to oncohematologic treatment by means of different scale. Review. *Med Oral Patol Oral Cir Bucal*. 2005;10:412-21.
12. Deslauriers N, Coulombe C, Carré B, Goulet JP. Topical application of a corticosteroid destabilizes the host parasite relationship in a experimental model of the oral carrier state of *Candida albicans*. *FEMS Immunol Med Microbiol* 1995; 11: 45-6.
13. Mosel DD, Bauer RL, Lynch DP, Hwang ST. Oral complications in the treatment of cancer patients. *Oral Dis*. 2011;17:550-9.
14. Elad S, Zadik Y, Hewson I et al. (2010). A systematic review of viral infections associated with oral involvement in cancer patients: a spotlight on Herpesviridae. *Support Care Cancer* 18: 993–1006.
15. Brown CG, McGuire DB, Peterson DE, Beck SL, Dudley WN, Mooney KH. The experience of a sore mouth and associated symptoms in patients with cancer receiving outpatient chemotherapy. *Cancer Nurs* 2009; 32: 259-70.
16. Hovan AJ, Williams PM, Stevenson-Moore P et al (2010). A systematic review of dysgeusia induced by cancer therapies. *Support Care Cancer* 18: 1081–1087.
17. Cheng KK. Oral mucositis, dysfunction, and distress in patients undergoing cancer therapy. *J Clin Nurs* 2007; 16: 2114-21.