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Original Article

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Insulin Induced Hypoglycemia during Chemotherapy as a Prelude to Treatment in Advanced and Recurrent Head and Neck Cancer: A Prospective Trial

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Abstract

Normal cells and cancer cells can be differentiated clearly during hypoglycemia because of the difference in the number of insulin receptors and the biologic response modification which insulin produces. This helps in targeting the chemotherapy drugs more specifically and effectively inside the cells. This occurs with reduced doses of chemotherapy drugs and minimizes their side effects. With this aim two patients with advanced and recurrent Head and Neck cancer were included in this pilot study and about one tenth the dose of chemotherapy with Carboplatin 75 mg and Gemcitabine 200 mg were given once weekly for six weeks during period of hypoglycemia produced every time by giving intravenous Insulin 0.1ug/kg. A complete response was achieved in one patient and other patient had a partial response and which responded to radiotherapy achieving a complete response. There was no side effect of the drug or hypoglycemia recorded by the patient. The survival was 11 months and 8 months respectively concluding that even one tenth the dose of chemotherapy given during hypoglycemia gives a very good clinical response with no side effects of the drugs.

Keywords: Insulin potentiation; Hypoglycemia; Low dose chemotherapy; Recurrent cancer.

Introduction

Chemotherapy drugs in high doses are required to force themselves across the cell membrane to produce powerful cell killing. This causes serious dose related side effects because chemotherapy agents do not discriminate between cancer cells and normal cells, killing both types of cells.

Dr. Donato Perez Garcia of Mexico in 1926[1] innovated new drug delivery technique called Insulin Potentiation Therapy (IPT). Insulin is a powerful harmone managing the delivery of glucose across the cell membrane. It communicates its messages to cells by joining up with specific insulin receptors scattered on the outer surface of the cell membranes. Every normal cell in human body has hundreds of receptors but cancer cells have 6 to 15 times more of such receptors. It is a well known fact that cancer cells have a voracious appetite for glucose and they virtually steal it away from the body's normal cells thus starving them. The excess of insulin receptors in cancer cells increases the permeability of cell membranes leading to increased intracellular concentration of chemotherapeutic drugs which is not seen in normal cells.[2,3]

Chemotherapy drugs like to attack rapidly dividing cells and in a tumor all cells are in different stages of cell cycle at one time. In a tissue culture experiment insulin along with insulin receptors stimulated growth in many of the cells that were not in the growth phase. This metabolic modification by insulin rendered more of these cells to chemotherapy attack contributing to increased death rate.[4,5]

Because of this important element of differentiation along with biologic response modification which insulin produces, very low doses of chemotherapy drugs get targeted more effectively inside the cancer cells. Cancer cells die; tumor shrinks and no side effects are seen in normal tissues. IPT appears to be wonderful new way of treating cancer using the conventional chemotherapy drugs in very

low doses.

Case report

A prospective study to know the actual effect of low dose of chemotherapy drugs during hypoglycemia was done. Patients with recurrent head and neck cancer who have nothing more to be offered were included in this study. A written informed consent regarding the procedure, including death due to hypo-glycaemia was obtained from the patients and their close relatives.

The aim was to achieve minimum blood sugar level of 50 mg% and to give one tenth dose of conventional chemotherapy drug during period of induced hypoglycemia and then normalize the blood glucose with oral and parentral glucose. Blood sugar levels, cardiac and neurological status was monitored before starting the treatment and also constantly during the period of hypoglycemia which lasted for about half hour. Chemotherapy was given every week for six weeks with close monitoring of disease and side effects of drugs and hypoglycemia.

This prospective pilot study included two patients of advanced and recurrent Squamous cell carcinoma of buccal mucosa. One patient had recurred after he underwent surgery and radiotherapy twice and the other had recurred after surgery and chemotherapy. Both these patients have nothing more to be offered except palliation so they were included in this trial.

Complete pretreatment evaluation was done for hematological, renal, hepatic, cardiac and neurological status which was normal in both patients. During chemotherapy patients were kept in intensive care unit with cardiac monitor and pulse oximeter on for continuous monitoring. Blood sugar was monitored closely during hypoglycemia phase for chemotherapy.

Premedication with Granicetron 3mg and dexona 8mg was given. Then Human Insulin 0.1mg/Kg was given intravenously. Blood sugar was done every 5 min and as soon as it was below 50 mg%, chemotherapy with Carboplatin 75 mg and Gemcitabine 200 mg were given as infusion over 15 min. Then oral fruit juices and dextrose 10% infusion were given and normal blood glucose was achieved. During period of hypoglycemia both patient had hot flashes, tachycardia, dryness of mouth, perspiration from which they recovered as soon as normal glucose level was achieved. There were no cardiac or neurological symptoms or signs recorded. Patients were fully conscious and oriented during the procedure. The same procedure and drugs were given every week for six weeks with close monitoring. During follow up period a close watch on the disease, cardiac and neurological status was kept. ECG was done during each visit to see any changes.

Fig 1: Pre treatment case of recurrent carcinoma buccal mucosa showing large growth

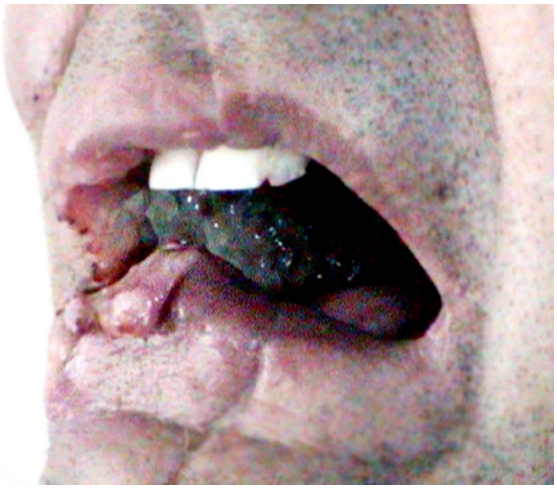
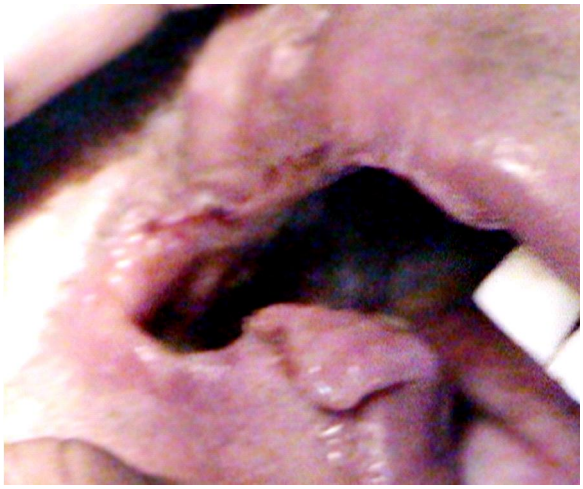


Fig 2: Six months post treatment showing complete regression of tumor with increase in size of oro cutaneous fistula



Results

Both patients had a good response to insulin potentiated chemotherapy. After completing six cycles one patient had a complete clinical response although there was increase in size of orocutaneous fistula and the other had a 75% reduction in size of tumor. Both the patients had tachycardia, perspiration, hot flushes and dryness of mouth which were temporary and reverted back to normal once the blood sugar was normal. None of the patients had any cardiac or neurological signs or symptoms either during the period of hypoglycemia or until their last follow-up. There was no Neutropenia, anemia, alopecia and loss of appetite seen as is routine with high doses of chemotherapy. Thus the tolerance to hypoglycemia was good with a good clinical response. One patient with partial response took radiotherapy and achieved a complete response. Astonishingly both the patients did not develop any nodal or distant metastasis during follow up, although no comments can be made on this aspect on this small study. The survival in these patients was eight months and eleven months respectively. The short term hypoglycemia did not have any cardiac or CNS side effects and is safe.

Discussion

IPT is a questionable cancer therapy that uses insulin as an adjuvant agent to potentiate the effect of chemotherapy. Advocates of IPT believe that cancer cells consume more sugar than healthy cells and therefore cancer cells are more sensitive to insulin and insulin like growth factor.[2,3] Insulin is also believed to increase the permeability of cell membrane increasing the intracellular concentration of anticancer drugs.[1] According to the theory behind the therapy, cancer cells contains ten times more insulin receptors in cell membrane and can be activated by exogenous insulin and one tenth dose of chemotherapy drug can provide the same cytotoxic effect with less severe adverse reaction. In multidrug-resistant metastatic breast cancer, methotrexate with insulin produced a significant antitumoral response that was not seen with either methotrexate or insulin used separately.[6] No clinical trial has been performed to validate this claim. Currently there is no data comparing the efficacy of I P T to conventional chemotherapy.

In our pilot study a definite clinical response with low doses of chemotherapy with insulin is seen meaning that there is an increased susceptibility of the cancer cells for chemotherapy drugs during hypoglycemia. Tolerance of patients to hypoglycemia is good with no side effects either early or delayed. Even there are no delayed cardiac or neurological side effects. So we conclude that good tolerance and a good clinical response in patients who have failed to all modalities of cancer treatment previously are achieved. So this method of drug delivery should be studied further and more randomized trials should be done to conquer the side effects of the drugs without compromising with the results.

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Original Article

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Pionears of Paediatric Oncology

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Abstract

Now days because of various factors malignancy incidences are increasing in all levels of socioeconomic strata of ccommunities. So the main aim of this article is that new generation of doctors should be aware of this all pionears including paediatricians.

Keywords: Oncology; Paediatrics; Pioneers; Old age.

2650 to 1950 BC

The first references of cancer goes back to this time, when in three Egyptian papyri detected the breast tumor together with a uterine carcinoma.[1]

1900-1600 BC

The earliest evidence of tumor was found in the skull of a female from Bronze Age period. [1]

(Egyptian papyri)

(Hippocrates)

460 BC-370 BC

Hippocrates was first to describe various kinds of cancer. As per Greek words 'carcinos' means- crab or crayfish. He described the

(Aurelius Cornelius Celsus)

(*Galen*)

appearance of cut malignant tumor as the veins stretched on all sides like the crab has its feet, so the name was kept. Also in Greek words swelling is known as oma, so he later add suffix and named as carcinoma.[1]

25 BC-50 AD:

Aurelius Cornelius Celsus translated carcinos into the Latin cancer, meaning crab. Also he described the phenomenon of metastatic process in malignancies.[1]

Claudius Galenus (Galen) (129–199 AD)

He was from Greek, who described benign tumors as "oncos" meaning as swelling. Also he was pioneer to introduce the term

(*Nicolaes Tulp*)

'sarcoma' from the Greek word 'sarca' (flesh). [1]

Wilhelm Fabry (1560 Jun 25-1634 Feb)

He was a German professor, who believed that breast cancer was caused by a milk clot in a mammary duct. [1]

Nicolaes Tulp (1593 Oct 09-1674 Sep)

He believed that cancer was a poison that slowly spreads and it was contagious.[2]

Francois de la Boe Sylvius (1614 May 11-1672 Nov 10)

He was a Dutch professor, who believed that all diseases were the outcome of chemical processes and acidic lymph fluid causes the

(*Wilhelm Fabry*)

(*Sylvius*)

(*Sir Percivall Pott)*

cancer.[2]

Jean Godinot (1661–1749)

He was a pioneer in starting the first cancer hospital in the world in Rheims (1740), which was dedicated to the cancer patients.[1]

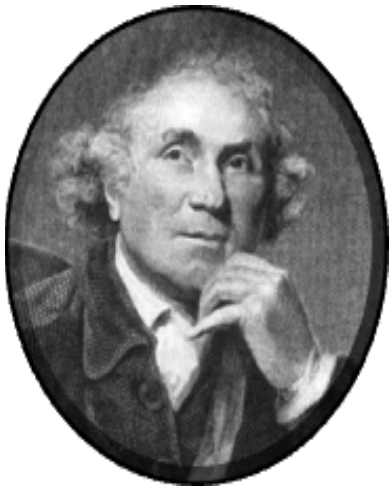
Sir Percivall Pott (1714 January 6 - 1788 December 22)

He was an English surgeon, first to demonstrate that a cancer may be caused by an environmental carcinogens.[3]

John Hunter (1787)

He was first to operate on metastatic melanoma.[1]

(*John Hunter)*



(*René Laennec)*

Rene Laennec (1804)

He was the French physician, who was first to describe melanoma as a disease entity. His report was initially presented during a lecture for the Faculte de Medecine de Paris and then published as a bulletin in 1806.[2]

Campbell Greig De Morgan (1811 November 22–1876 April 12)

He was a British surgeon who first mentioned that cancer arose locally and then spreads first to the lymph nodes and then more widely in the body.[4]

Thomas Hodgkin (1832)

He was a pathologist, first to described a

(*Thomas Hodgkin)*

(John Templeton Bowen)

form of lymphoma, which was named as of Hodgkin's disease.[5]

John Templeton Bowen (1857–1940)

He was an American dermatologist, who named Bowen's disease and Bowenoid papulosis.[1]

William Coley (1862 January 12-1936 April 16)

He was an American bone surgeon and cancer researcher, pioneer of cancer immunotherapy. In 1968, he identified an alpha tumor necrosis factor.[5]

Rudolf Virchow (1864)

A German physician who was first to describe an abdominal tumor in a child as a

(Rudolf Virchow)

"glioma" The characteristics of tumors from the sympathetic nervous system and the adrenal medulla were then noted in 1891 by German pathologist Felix Marchand.[6]

James Stephen Ewing (1866 December 25-1943 May 16)

He was an American pathologist, who discovered a form of malignant tumor which is known as EWING SARCOMA. [1]

Ludwig Pick (1868–1944)

He coined the term Pheochromocytoma in 1912 and described the chromaffin color change in tumor cells associated with adrenal medullary tumors. [1]

(William Coley)

(Ludwig Pick)

(Emil Herman Grubbe)

James Homer Wright (1869 April 8-1928 January 3)

He was an American pathologist, who was chief of pathology at Massachusetts General Hospital. He is the same "Wright" for which Wright's stain, and the "Homer Wright rosettes" associated with neuroblastoma.[6]

Emil Herman Grubbe(1875 January 01-1960 March 26)

Emil Herman Grubbe -He was the first American to use x-rays the for treatment of cancer.[7]

Frankel (1886)

Frankel made the first description of a patient with Pheochromocytoma.[1]

(Marie Curie)

Marie Curie and Pierre Curie (19th century)

Marie Curie and Pierre Curiediscovered radiation, the first effective non-surgical treatment of cancer patients.[3]

Theodor Boveri (1902)

He was a German professor of zoology at Munich, who identified the genetic basis of cancer. He studied that mutations of the chromosomes can generate a cell with unlimited growth potential which passes onto its descendants. He proposed the existence of tumor suppressor genes and oncogenes, also mentioned that cancers might be caused or promoted by radiation, physical or chemical insults or by pathogenic microorganisms.[4]

(Pierre Curie)

(Theodor Boveri)

(Dr Sidney Farber)

J. J. Thompson (1903)

He discovered the presence of radioactivity in well water. That's why preparations of radium salt in bath water was suggested as a way for patients to be treated at home, as the radio-activity in the bathwater was permanent. Radium baths became used experimentally to treat arthritis, gout, and neuralgias.[3]

Dr Sidney Farber (1903–1973)

He was a paediatric pathologist, who is regarded as the father of modern chemotherapy. He evaluated the role of aminopterin as a folate antagonist in childhood acute lymphoblastic leukemia. He showed for the first time that induction of clinical and hematological remission in this disease was achievable.[8]

(Max Wilms)

Niels Finsen (1905)

He discovered that lupus was amenable to treatment by ultraviolet rays when separated out by a system of quartz crystals, and thereafter created a lamp to sift out the rays. The Finsen lamp became widely used in for phototherapy. Finsen was soon awarded a Nobel prize for his research.[1]

Max Wilms (1910)

He was pioneer in the study of tumor cells originating during the development of the embryo, known as "nephroblastoma" or Wilms' tumor. This is a malignant tumor of the kidney. He did extensive work in the field of radiology, using radiation therapy for treatment of tumors and tuberculosis.[1]

(*Niels Finsen*)

(Patrick S.)

Roux & Mayo (1926)

Roux (in Switzerland) and Mayo (in U.S.A.) were the first surgeons to remove pheochromocytomas.[1]

Janet Lane-Claypon (1926)

He observed that the bone marrow of victims of the atomic bombs of Hiroshima and Nagasaki was completely destroyed. From these observations, he concluded that diseased bone marrow could also be destroyed with radiation and this led to the development of bone marrow transplants for leukemia.[1]

Charles Heidelberger (1950)

He synthesized the fluoropyrimidine 5-fluorouracil, which had a broad-spectrum activity against various types of solid tumors.[10]

Patrick S. Moore (1956 October 21)

He was an American virologist who co-discovered together with his wife, Yuan Chang, two different human viruses causing the AIDS-related cancer Kaposi's sarcoma and the skin cancer Merkel cell carcinoma.[11]

Yuan Chang (1959 November 17)

She was an American virologist and pathologist who co-discovered the two human cancer viruses-Kaposi's sarcoma associated herpes virus and Merkel cell polyomavirus. [12]

(Yuan Chang)

Copp and Cheney (1962)

They purified Calcitonin and was considered as a secretion of the parathyroid glands, later identified as the secretion of the C-cells of the thyroid gland.[13]

DeVita VT, Moxley JH, Brace K, Frei E III (1965)

They developed for the first time the MOMP program for Intensive combination chemotherapy and X-irradiation in the treatment of Hodgkin's disease.[14]

Anthony Epstein, Bert Achong and Yvonne Barr (1968)

Anthony Epstein, Bert Achong and Yvonne Barr identified the first human cancer virus, called the Epstein - Barr virus.[14]

HeLa. Gold, Michael (1973)

He discovered oncoviruses.[15]

Harald zur Hausen (1984)

He discovered first human papillomaviruses -HPV16 and HPV18, which were responsible for cervical cancers. For this discovery, he was honored with Nobel Prize in 2008.[1]

(Sir Michael Anthony Epstein)

(Harald zur Hausen)

1980

Paediatric oncology as a specialty was virtually nonexistent in the India. Most children were treated by adult oncologists. The first dedicated paediatric cancer unit was started in Tata Memorial Hospital in 1985.[15]

John A. Boockvar (2009)

An American neurosurgeon, who performed the world's first intra-arterial delivery of the high-potency chemotherapeutic agent Avastin (bevacizumab) directly into a malignant brain tumor. He started a new era of "interventional neuro-oncology.[16]

(John A. Boockvar)

Fathers figures of cancer pathology

Giovanni Battista Morgagni, Marie-Francois Xavier Bichat, Johannes Muller and Rudolf Ludwig Karl Virchow were known as father figures of cancer pathology. They were the first to describe microscopically the appearance of malignant tumors, the tumor stroma, the pathways of metastases and the association of inflammation and cancer.[17]

History of radiotherapy

1869: The 'cathode rays' were discovered by Hittorf.

1895: Roentgen made the first X-ray photo.

1896: Voigt in Germany irradiated the first

(Giovanni Battista Morgagni)

(1682–1771: from Padua)

(Marie-Francois Xavier Bichat)

(1771–1802: from France)

(Johannes Muller)

(1801–1858)

(Rudolf Ludwig Karl Virchow)

(1821–1902: from Germany)

patient with a cancer of the throat.

1939: Cyclotron was invented.

1940: Betatron was invented.

1948: Cobalt-60 unit was invented.

1953: Brachytherapy and linear accelerator was invented.

History of Chemotherapy

460–370 BC: Hippocrates's remedy was a mixture of momordica elaterium, cucumber honeycomb and water in juice was used for treatment of cancer.

100AD: Dioscurides of Anazarous used terebinth oil, frankincense, hedge mustard and honey in plasters for hidden cancers.

100AD: Leonides of Alexandria used ass's milk, opium, pork fat, fresh butter and rose oil in plasters for cancer treatment.

200AD: Galen of Pergamum used an ointment consisting of calcined shells of whelk, purple shell fish, oysters, sea urchin, crab, sour wine, honey, pork fat for external cancers.

1900: German chemist Paul Ehrlich coined the term "chemotherapy".

Dr. Min Chiu Li (1968): He was a pioneer chemotherapist who developed new curative chemotherapy for metastatic choriocarcinoma and testicular cancer.

20th century: The use of chemotherapy for the treatment of cancer began.

1910: George Clowes of Roswell Park Memorial Institute in New York, developed the first transplantable tumor systems in rodents.

(Hittorf)

(Paul Ehrlich)

Gustaf Lindskog (1946): He was a thoracic surgeon, who administered nitrogen mustard to a patient with non–Hodgkin's lymphoma having severe airway obstruction. Marked regression was observed in this and other lymphoma patients. The use of nitrogen mustard for lymphomas spread rapidly throughout the United States after the publication of this article.

1949: Farber, Heinle and Welch tested folic acid in leukemia and they came to the conclusion that it actually accelerated leukemia cell *growth.*

1950: Penicillin was initially thought to have antitumor properties that were never confirmed. But later on another antibiotic, actinomycin D was studied for antitumor properties and which is commonly used in pediatric tumors.[18]

1948: Farber showed the antifolate activity of methotrexate in childhood leukemia.

Despite all these inventions and modalities of management, the morbidity and mortality related with paediatric malignancies is challenge to forthcoming paediatricins and paediatric oncosurgeons. The important massage by this "*History Of Paediatric Oncology" i*s to relieve pain of child and his family due to malignancy.

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Review Article

Multilingual Validation and Cross-Cultural Adaptation of European Organization for Research and Treatment of Cancer- Quality of Life Questionnaire 30-Item Core Version (EORTC-QLQ-C30): An Update

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Abstract

The European Organization for Research and Treatment of Cancer- Quality of Life Questionnaire 30-Item Core Version (EORTC-QLQ-C30) is globally regarded as a gold-standard self-reported evaluation tool for Health-related quality of life (HRQoL) for use in cancer practice, education, research and administration. The objective of this review article was to address its applicability in various languages through studies on cross-cultural adaptation and translation-validation. There were 19 studies found on 13 languages (Chinese=4; Turkish=3; Taiwan Chinese=2; other ten languages=1 each), all of them reporting acceptable reliability, validity and responsiveness for the translated versions of EORTC-QLQ-C30 for evaluating HRQoL in cancer patients in a variety of settings and situations. There is need for validating EORTC-QLQ-C30 questionnaire into Indian languages to facilitate its routine use in oncology and palliative care settings.

Keywords: Oncological evaluation; Quality of life; Psychooncology; EORTC-QLQ-C30.

The European Organization for Research and Treatment of Cancer- Quality of Life Questionnaire 30-Item Core Version (EORTC-QLQ-C30) is globally regarded as a gold-standard self-reported evaluation tool for Health-related quality of life (HRQoL) for use in cancer practice, education, research and administration. The objective of this review article was to address its applicability in various languages through studies on cross-cultural adaptation and translation-validation.

Chinese

Cheng *et al*[1] administered the EORTC QLQ-C30 (version 3.0) at three time points: T1, the first or the second day that patients were hospitalized after the brain tumor suspected or diagnosed by MRI or CT; T2, 1 to 2 days after T1, (T1 and T2 were both before surgery); T3, the day before discharge. The authors found that Cronbach's alpha coefficients for multi-item scales were greater than 0.70 and most of the item-scale correlation coefficients met the standards of convergent and discriminant validity, except for the cognitive functioning scale.

Wan *et al*[2] used the simplified Chinese version of the QLQ-C30 on 600 patients with five types of cancer: lung, breast, head and neck, colorectal, and stomach, and found good construct validity with the alpha coefficients for all domains >0.7 except for cognitive functioning; and test-retest reliability coefficients for most domains >0.80 except for appetite loss and diarrhea.

Zhao and Kanda[3] studied 191 gynecological cancer patients including gestational trophoblastic disease patients (n = 68), ovarian cancer patients (n = 105), and other types of gynecological cancer patients (n = 18) and found that all item-subscale correlation coefficients exceeded the criterion of item-convergent validity except item 1, 5, 20, and 25, and all items correlated

significantly higher with their own subscale than with other subscales except item 1, 20, and 25. The correlation coefficients among all subscales were significant but modest, with seven out of nine subscales meeting the minimal standards of reliability.

Zhao and Kanda[4] studied 143 patients with breast, gynecological, or lung cancer in six hospitals in China, and found that Cronbach's alpha coefficients for multi-item scales were greater than 0.70 before and during treatment, except for the cognitive functioning scale. Most of the item-scale correlation coefficients met the standards of convergent and discriminant validity. All scales and items were found to exhibit good reproducibility, criterion-related validity, and construct validity.

English

Luo *et al*[5] studied a heterogeneous sample of 57 cancer patients and found that Spearman's correlations between the QLQ-C30 and SF-36 scales ranged from 0.35 to 0.67, with Cronbach's alpha ranging from 0.19 for the cognitive functioning scale to 0.91 for the global QoL scale.

Greek

Kontodimopoulos *et al*[6] studied 105 female breast cancer patients to assess construct validity and internal consistency reliability of the Greek EORTC QLQ-C30 and found, item convergence rate was 92% and discrimination rate was 87%. Cronbach's alpha for all subscales was >0.70 except for cognitive functioning. Correlation with SF-36 ranged from 0.25 to 0.64,

Indonesian

Perwitasari *et al*[7] studied 128 cancer patients undergoing cisplatin chemotherapy regimen and found internal consistency with values of >0.70. All items in the questionnaire met the criteria of convergent and discriminant validity, except for item 5. Moderate correlations were observed with SF-36 Indonesian version.

Iranian (Persian)

Montazeri *et al*[8] studied 168 breast cancer patients and found Crohnbach's alpha for multi-item scales ranged from 0.48 to 0.95 at baseline and from 0.52 to 0.98 at follow-up. Fair to good inter-scale correlations and all functioning and symptom scales were found to discriminate between subgroups of patients differing in clinical status as defined by their performance status and disease stage.

Japanese

Kobayashi *et al*[9] studied 105 lung cancer patients and found that the Japanese QLQ-C30 has a weak scale of role functioning in terms of item discriminative validity and a weak scale of cognitive functioning in items of discriminative validity and internal consistency.

Korean

Yun *et al*[10] studied 170 patients and found that all scales met multidimensional conceptualization criteria, in terms of convergence and discrimination validity. Cronbach's alpha coefficients for eight multiple-item scales were greater than 0.70, with the exception of cognitive functioning. Good interscale correlations were observed, with physical and emotional functioning being explanatory variables for the global quality-of-life (QOL) scale.

Polish

Tomaszewski *et al*[11] studied 98 patients with esophagi-gastric cancer and found that Polish version of the EORTC QLQ-C30 was a reliable and valid tool for measuring health-related quality of life.

Spanish (Mexican)

Cerezo *et al*[12] studied 234 Mexican

women with breast cancer and found adequate Convergent and divergent validity, Cronbach's alpha of all multi-item scales showed values e"0.7 except for Cognitive functioning subscale, and patients with early stages had better functional scores and lower symptoms scores than patients with chronic/ advanced stages.

Sinhala

Jayasekara *et al*[13] studied 489 pre-treatment and 343 during-treatment cancer patients and their findings supported the scale structure of the QLQ-C30, with the exception of the cognitive functioning scale, moderate interscale correlations and good discriminative properties.

Taiwan Chinese

Chie *et al*[14] studied 51 lung cancer patients undergoing active chemotherapy and 48 such patients undergoing follow-up and found that the intraclass correlation between test and retest ranged from 0.46 to 0.85 for the QLQ-C30. The kappa coefficients between test and retest ranged from 0.51 to 0.73 for single items of the QLQ-C30. The Cronbach's alpha coefficients were > or = 0.70 for all scales apart from that of cognitive functioning. The correlation coefficients between indices measuring similar dimensions of the EORTC QLQ-C30 and the SF-36 questionnaires ranged from 0.43 to 0.73.

Chie *et al*[15] studied 35 breast cancer patients under active treatment and 54 under follow-up and found that the intraclass correlation coefficient was moderate to high in the follow-up group. The Cronbach's alpha coefficients of most scales were > or = 0.70 except that of physical functioning, cognitive functioning, and arm symptoms. Correlations of scales measuring similar dimensions of the EORTC QLQ-C30 and the SF-36 were moderate.

Thai

Silpakit *et al*[16] studied 310 cancer patients and found that "Cronbach's alpha coefficients of the six scales were above 0.7, except for cognitive and social function scales. All test-retest reliability coefficients were high. Multi trait scaling analysis showed that all item-scale correlation coefficients met the standards of convergent and discriminant validity. Most scales and items could discriminate between subgroups of patients with different clinical status assessed with the Eastern Cooperative Oncology Group (ECOG) scale."

Turkish

Guzelant *et al*[17] studied 202 lung cancer patients and found that all the subscales met the minimal standards of reliability (Cronbach's alpha > or = 0.70), and only the role functioning scale differed among the three disease stages of patients (local, locoregional and metastatic). "All interscale correlations were present, with the strongest correlations found among the physical functioning, role functioning and fatigue scales. Social functioning was closely related with physical, role, emotional and cognitive functioning. The weakest correlations were between nausea/ vomiting and the other scales. Global quality of life (QOL) was substantially correlated with most of the scales except cognitive functioning."

Hoopman *et al*[18] studied 90 Turkish and 79 Moroccan patients and found strong convergent validity for all multi-item scales, high internal consistency except for cognitive functioning, good discriminant validity to distinguish clearly between subgroups formed on the basis of performance status and comorbidity, and was moderately responsive to change over time in performance status.

Demirci *et al*[19] studied 127 breast cancer patients undergoing radiotherapy and found that six of the 8 multi-item scales of QLQ-C30 had a high reliability where physical functioning and pain scores were less reliable. The most determinative subscales of QLQ-C30 on global health were emotional functioning followed by fatigue, role functioning and appetite loss.

There were 19 studies found on 13 languages (Chinese=4; Turkish=3; Taiwan Chinese=2; other ten languages=1 each), all of them reporting acceptable reliability, validity and responsiveness for the translated versions of EORTC-QLQ-C30 for evaluating HRQoL in cancer patients in a variety of settings and situations. There is need for validating EORTC-QLQ-C30 questionnaire into Indian languages to facilitate its routine use in oncology and palliative care settings.

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Sebaceous Carcinoma of the Extremity: A Case Report

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Abstract

Sebaceous Carcinoma is an uncommon, aggressive malignant tumor derived from the adnexal epithelium of sebaceous gland either from ocular or extra ocular sites. Extra ocular sites being very uncommon and forms one-fourth of all sebaceous carcinomas. Patients presenting in extremity are rarest and have a high mortality rate. Here we present one case which presented with multiple orange colored nodular lesions over dorsum of right hand, it recurred and progressed very fast after surgery and no response was seen with chemotherapy.

Keywords: Upper extremity; Sebaceous carcinoma.

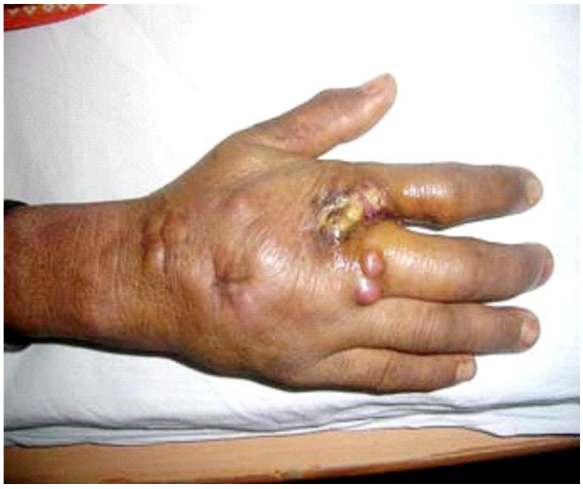
Introduction

Sebaceous carcinoma is an aggressive tumor derived from the adnexal epithelium of sebaceous glands and accounts for 1% of all cutaneous malignancies. These glands have a wide spread distribution in the skin but the tumor arises mainly in ocular adnexa and less commonly in extra ocular sites. Extra ocular sebaceous carcinoma comprises only 25% of all sebaceous carcinoma[1] involving mainly the head and neck region in which sebaceous glands are in plenty followed by external genitalia, parotid and submandibular glands, external auditory canal, trunk, upper extremity, sole and laryngeal and pharyngeal cavities in this order.[2] It may also occur in Muir Torre Syndrome (MTS) characterized by occurrence of sebaceous tumors in association with visceral malignancies.[3] A case of rapidly growing right upper extremity Sebaceous Carcinoma is presented here.

Case history

A 65 years old female presented with a non tender swelling over dorso-medial aspect of proximal interphalangeal joint of right Index finger. Excision of this swelling was done and the histology was inconclusive. She presented two months later with a recurrence and had developed multiple orange colored nodular lesions over dorsum of right hand and in the web between index and middle finger (Fig 1). These nodules were firm to hard and fixed to skin. Her past medical history was unremarkable and there was no family history of similar lesions or any other malignancy. Excision biopsy of one nodule was done which showed groups and strands of finely vacuolated and foamy cells showing clear to eosinophilic cytoplasm infiltrating in the stroma (Fig 2, 3). Based on the clinical picture and histology a diagnosis of sebaceous carcinoma of right upper extremity was established. The patient presented one month after excision with progressive disease and pain in arm. She has developed one 2x2 cm firm orange colored nodular growth over lateral aspect of right forearm and 3 to 4 other orange subcutaneous nodules over lower medial aspect of right arm. There was a 3x3 cm firm, mobile right axillary lymph node (Fig 4). Other lymph node was not palpable. A thorough investigation including CT Scan thorax and abdomen, triple endoscopy and colonoscopy

Fig 1: Multiple orange colored nodular lesions over dorsum of hand



done were within normal limits. As patient denied surgery she was started on with palliative chemotherapy with which she had pain control but there was no response to chemotherapy after three cycles combination chemotherapy with cisplatin75mg/m^2 day 1 and Ifosphomide 1.2 gm/m^2 day 1 to 3 given every three weeks. The patient tolerated the chemotherapy well and did not have any haematologic or bladder toxicity. Later the patient was lost to follow-up.

Discussion

Extra ocular sebaceous carcinoma involving the extremity is very uncommon, aggressive malignant tumor arising from sebaceous glands. Mean age of occurrence is 63 years involving both sexes in equal proportion. The prognosis depends on size, color and site of the lesion. Ocular lesions more than 1cm with red flags have unfavorable prognosis.[2] Our patient also presented at 65 years age and the larger lesions showed similar poor prognosis. The disease exhibits a variety of clinical presentation that the diagnosis is often delayed for months to years.[4] It may appear on the top of pre-existing dermatoses like naevus sebaceous and actinic keratosis or may follow radiation therapy received for other diseases. [5,6,7] It may also occur in MTS, which is characterized by occurrence of sebaceous tumor in association with visceral malignancies.[3] Although our patient did not

Fig 4: Orange colored nodular growth over right forearm and 3 to 4 other orange subcutaneous nodules over arm

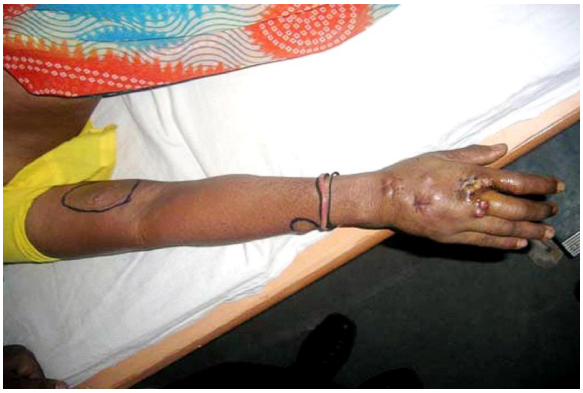
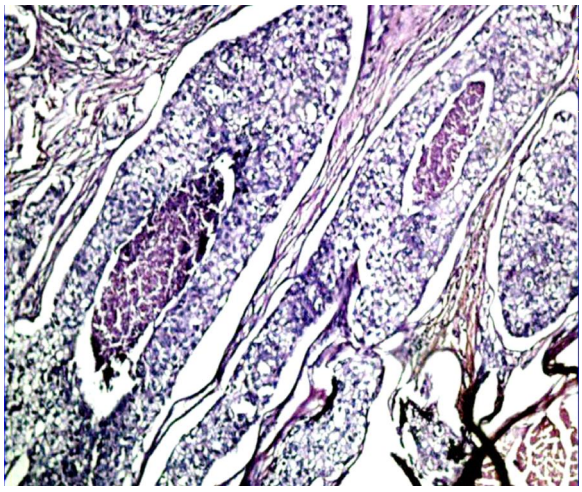
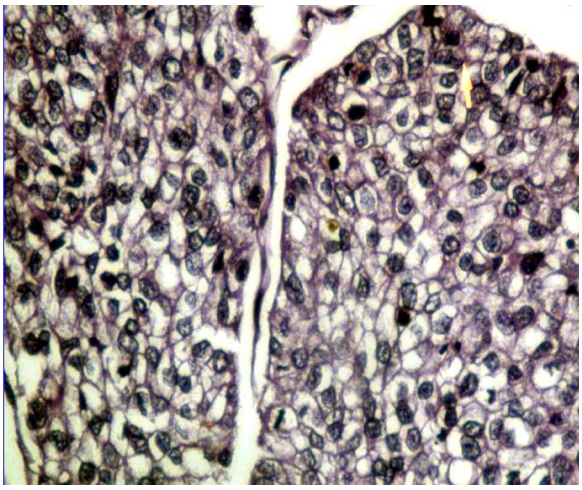


Fig 2 and 3: Groups and strands of finely vacuolated and foamy cells showing clear to eosinophilic cytoplasm infiltrating in the stroma (Mag 10x & 40x)





have a positive family history or presence of any internal malignancy.

The lesions usually present as pink to red yellow nodular growth in skin and may clinically resemble pyogenic granuloma, haemangioma or squamous cell carcinoma. The draining lymph nodes may be involved in few cases only.[8] Ghosh et al also found a moist, yellowish pink cauliflower-like oval shaped growth on the pinna with mild bleeding and some purulent discharge.[4]

Regardless of the location this malignancy is highly aggressive with a potential for regional and distant metastasis. Our patient also presented with orange nodular lesions and progressed very fast involving the lymph nodes, although no distant metastasis was seen. There were no signs of internal visceral malignancy.

Criterion for the diagnosis of MTS includes the presence of at least one sebaceous adenoma, epithelioma or sebaceous carcinoma and at least one visceral cancer in the absence of other participating factors such as Radiotherapy and AIDS.[9] However Immunohistochemistry, an important aid to the diagnosis of MTS could not be performed on the tumor in our patient due to local non-availability of the facility and patients financial constraints.

Treatment of sebaceous carcinoma requires wide local excision with removal of involved regional lymph nodes. But Nelson showed that chances of local recurrence are very high as is seen in our patient also.[2] Bailet reported a review of 92 patients with extra ocular sebaceous carcinoma and found a recurrence rate of 28% and metastasis in 21% of cases after local excision.[10] Radiation therapy has been considered as an adjunctive or palliative treatment but is generally not recommended as a primary treatment. The role of chemotherapy has not been defined due to scarcity of these lesions.

Due to multicentricity of the lesion we started the treatment with chemotherapy, as wide local excision was not possible. The patient has a partial response with the first cycle of chemotherapy using cisplatin and Ifosphamide combination. After three cycles of chemotherapy we did not see any response in the tumor instead it progressed and involved the skin of chest wall although till last follow up there were no distant metastasis.

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Quality of Life in People with Cancer Pain: An Overview of Reviews

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Abstract

The objective of this short communication was to inform evidence through an overview of reviews of cancer pain and quality of life. Theoretical understanding of cancer pain should involve a combination of biochemical/neurobiological factors, together with social/racial and ethnocultural influences of pain and quality of life in people with cancer. Both generic and disease-specific self-reported questionnaires should be used to explore utility and efficacy of interventions and also to study the multidimensional impact of cancer pain on quality of life. Multimodal management with treatment options ranging from educational, medical/ pharmacological (bisphosphonates), surgical (nerve blocks) and radiation therapy should be incorporated into supportive cancer care. Future research should address caregiver and family issues, and explore the mechanism-based paradigm in cancer pain in order to effectively enhance quality of life of people with cancer pain.

Keywords: Palliative oncology; Cancer anesthesiology; Quality of life; Cancer pain.

Knopp *et al*[1] explained that most cancer patients will experience moderate to severe pain and/or neuropathy during the course of their disease or its treatment. Whilst individually tailored medical management is useful, use of supportive care approaches is essential by combining mechanistic methods into knowledge of endophenotypesfrom the cancer patient's perspective, the biochemical/ neurobiological sequalae associated with tumor growth and therapies designed to arrest tumor progression so that effective treatment of cancer-related pain, sensory neuropathies, and associated endophenotypes could be achieved to preserve QoL.

Gordon[2] explained the ethnocultural influences of pain on quality of life in people with cancer, from the family and patient background and their role in interpersonal shared informed decision-making in therapeutic goal setting and implementation strategies.

Payne *et al*[3] searched Medline and performed a qualitative literature review to identify racial disparities in the palliative care of patients with cancer and their impact on quality of life for African-American women, which concluded; "Differences in treatment patterns, pain management, and the use of hospice care exist between African-American women and women in other ethnic groups. In addition, the emotional, social, and other aspects of quality of life for African-American women with breast cancer are not well understood, in part due to the absence of a standardized quality-of-life measure."

Bonomi *et al*[4] searched MEDLINE, PSYCHLit, and CANCERLitto identify QoL instruments that included a pain subscale or pain-related itemsavailable for use in assessing the impact of pain on the quality of life (QoL) of cancer patients, and methods to evaluate

the appropriateness of these QoL measures. The study foundscores of measures including utility measures that measure general QoL and condition-specific instruments to measure the impact of specific conditions, such as cancer, on QoL.

Lipton[5] suggested analgesic drugs for first line of pain relief in cancer, together with nerve blocks and other procedures which are to be early with conviction and persistence.

Ling *et al*[6] searched six databases (Medline, CIHAHL, PubMed, EMBASE, PsycINFO and DARE) for randomized controlled trial studies of pain-education programmes for cancer patients and found four studies that reported reductions in pain intensity and pain interference, but not in quality of life.

Di Lorenzo *et al*[7] studied the efficacy of External beam radiation therapy (EBRT)for pain relief and improvement in quality of life (QoL) in 75 patientswith bone metastases from prostate cancer, who were also administered second-line hormonal therapy (HT) in 20 patients, chemotherapy (CT) in 25 patients, biphosphonates in 45 patients. EORTC QLQ-C30 questionnaire scores and pain scores improved in all the groups which suggested that EBRT was an effective and safe treatment modality.

Diel[8] emphasized that bisphosphonates offer significant and sustained relief from bone pain and can also improve quality of life in patients with metastatic breast cancer. High-dose bisphosphonates can offer rapid relief of acute, severe bone pain, instead of waiting for the pain to become unbearable or associated with pathological fractures.

Esperand Redman[9] suggested need for future research on management of fatigue and urinary symptoms in addition to control of pain from bone metastasesin patients with prostate cancer. Caregiver burden and end-of-life caresignificantly affect quality of life, thereby presenting challenges to supportive care and pain management by health care providers.

Mantyh[10] opined, "Developing a mechanism-based understanding and mechanism-based therapies to treat cancer-associated pain and sensory neuropathy, and incorporating these into mainstream cancer research and therapy, will be crucial to improving the quality of life and survival of patients with cancer." Can mechanism-based classification[11] and its ensuing mechanism-based therapy[12] be the elixir to enlighten the lives of people with cancer pain towards enhanced quality of life?

Theoretical understanding of cancer pain should involve a combination of biochemical/ neurobiological factors, together with social/ racial and ethnocultural influences of pain and quality of life in people with cancer. Both generic and disease-specific self-reported questionnaires should be used to explore utility and efficacy of interventions and also to study the multidimensional impact of cancer pain on quality of life. Multimodal management with treatment options ranging from educational, medical/pharmacological (bisphosphonates), surgical (nerve blocks) and radiation therapy should be incorporated into supportive cancer care. Future research should address caregiver and family issues, and explore the mechanism-based paradigm in cancer pain in order to effectively enhance quality of life of people with cancer pain.

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[1] Flink H, Tegelberg Å, Thörn M, Lagerlöf F. Effect of oral iron supplementation on unstimulated salivary flow rate: A randomized, double-blind, placebo-controlled trial. J Oral Pathol Med 2006;35:540-7.

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Article in supplement or special issue

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Unpublished article

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Reference from electronic media

[9] National Statistics Online—Trends in suicide by method in England and Wales, 1979-2001. www.statistics.gov.uk/downloads/theme_health/HSQ 20.pdf (accessed Jan 24, 2005): 7-18. Only verified references against the original documents should be cited. Authors are responsible for the accuracy and completeness of their references and for correct text citation. The number of reference should be kept limited to 20 in case of major communications and 10 for short communications.

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