Incidence of Neutropenia in Locally Advanced Esophageal Carcinoma treated with concurrent chemoradiation

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ABSTRACT

Objective: To analyse incidence of neutropenia in locally advanced esophageal carcinoma treated with cisplatin & 5 flurouracil based chemo radiation. **Methods:** This descriptive case series study was conducted in the Department of Clinical Oncology LINAR Cancer Hospital Larkana from January 2016 to August 2017 ,on histological proven squamous cell carcinoma of esophagus with Inclusion criteria locally advanced stage, good performance status (ECOG-0,01,02),normal blood counts, normal hepatic & renal profiles. Exclusion criteria with carcinoma of cervical esophagus, infiltration of tumor in tracheobronchial tree, distant metastasis. We planned our patients with EBRT have total dose of radiation 50.4Gy in 28 fractions. Inj Cisplatin 75mg/m2 IV D1 & Inj 5- Flurouracil 1000mg/m2 IV D1 to D4 were infused during 1st & 5th week of external beam radiotherapy & 8th & 11th weeks. Neutropenia was assessed on weekly basis through complete blood counts(CBC) during course of con current chemoradiation & later on during two cycles of adjuvant chemotherapy infused after chemoradiation. Neutropenia grading were performed on basis of common Terminology Criteria for Adverse Events (CTC AE).The data was statistically analyzed. **Results:** Majority of patients have age above 40 years. The average age of patients & duration of disease were $46.45^{+/-}$ 10.59 years(95%CI :46.45+/- 10.59) and 3.5 +/-1.17 months(95%CI:3.20 to 3.80) respectively.out of 62 cases 27(43.5%) were male & 35(56.5%) were female. Chemoradiation induced neutropenia was assessed on complete blood counts on weekly basis. Neutropenia grading were performed. Neutropenia grading from grade 1 to 4 were 2%,34%,48%,16% cases respectively**. Conclusion:** Chemotherapy induced neutropenia is most common oncological emergency. It increases morbidity and mortality if not assessed timely during cancer treatment.**Key words:** Esophageal carcinoma, Neutropenia, Chemoradiation, Filgristim,Cisplatin,5 flurouracil

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INTRODUCTION:

Esophageal carcinoma is a highly lethal malignant tumor with a poor prognosis. Esophageal carcinoma is 8th most common malignant tumor and ranking 6th most common cause of oncological mortality worldwide.[1,2,3] Esophageal carcinoma is a malignant disease with wide range of global variation in its incidence.[4] Esophageal carcinoma is the sixth common malignant neoplasm reported in Pakistan.[5] According to KIRAN Cancer registry (KCR) report there were 19559 cancer patients registered from 1st January 2000 to 31st December 2009 in which 743 (3.8%) patients were suffering from carcinoma of esophagus with gender ratio of 395 and 348 males and females respectively.[6]Esophageal carcinoma may

be classified as either squamous cell carcinoma or adenocarcinoma while less common histologies include adenoid cystic carcinoma, muco epidermoid carcinoma, small cell carcinoma, lymphoma and leiomyosarcoma.[7]Squamous cell carcinoma accounts 90% of esophageal cancer in China.[8]Despite much technical advancement carcinoma of esophagus still remains a therapeutic challenge. The majority of patients with carcinoma of esophagus are diagnosed in advanced stage i-e III-IV.[9]Surgery remains mainstay of treatment. Three years survival rate after radical surgery is 20% and post surgical mortality rate is 3 to 10%.[10]Patients who are surgical inoperable or denied for esophagectomy, concurrent chemo radiation is treatment of choice. The neo adjuvant & definitive chemo radiation in carcinoma of esophagus improve patients overall survival in comparison to esophagectomy alone.[11,12,13]

Nowadays there are various chemotherapy regimens such as Cisplatin & 5 flurouracil (CF), paclitaxel & carboplatin (PC),docetaxel, cisplatin & 5 flurouracil (DCF) are used in neo adjuvant and during definitive chemo radiation of carcinoma of esophagus. The disease free survival and median overall survival with these chemotherapy regimens were 09 months & 17 months respectively.[14]These chemotherapy regimens results high risk of neutropenia grade III-IV, thrombocytopenia grade III-IV, diarrhea grade II-III, vomiting grade II,III,IV and esophagitis Neutropenia is most life threatening oncological emergency. Neutropenia is defined as an an absolute neutrophil count (ANC) less than 1500 per microliter. Neutropenia is graded mild, moderate and severe on basis of ANC which is calculated on CBC. Neutropenia is routinely diagnosed on complete blood counts. Severe neutropenia is defined as ANC of less than 500 per microliter. Febrile neutropenia is defined as ANC less than 500 per microliter and patient has an oral temperature more than $101F^0$ ($38.3\ C^0$) or has two consecutive readings greater than$100.4\ F^0$ ($38.0\ C^0$) for two hours. Neutrophil has life span of three days. Nueutropenia usually occur at 03 to 07 days after cancer chemotherapy infusion. Neutropenia management is based upon neutropenia grade, underlying risk factors, comorbid and performance status of cancer patients. Neutropenic patients are more susceptible for developing bacterial, fungal and viral infections, if not timely address can leads septicemia resulting in death.[15] infections Neutropenia can be managed with preventive measures, prophylactic use of antibiotics and granulocyte colony stimulating factor(G-CSF).In cancer patients neutropenia results increase mortality rate and economic cost of treatment.[16,17]

METHODS:

This descriptive prospective case series study was conducted in the Department of Clinical Oncology LINAR cancer Hospital Larkana from January 2016 to August 2017.We have enrolled sixty two patients by non probability sampling, on histological proven squamous cell carcinoma of esophagus staged radiologically T3-T4,No,-1,Mo according to TNM Classification, ECOG performance status 0,1 or 02,normal hematologic profile & normal function of liver and kidney by routine laboratory examination (i-e CBC, LFT,RFT).While exclusion criteria were adenocarcinoma of

esophagus, carcinoma of cervical esophagus, carcinoma of gastro esophageal junction, patients with esophageal biopsy of lymphoma, leiomyosarcoma, adenocystic carcinoma, small cell carcinoma, infiltrations of tumor into tracheobronchial tree, distant metastasis (i-e liver, adrenal glands).Radiation planning was performed on 2 dimensional external beam radiotherapy technique. Gross tumor volume and nodal involvement were delineated through CT scan neck, chest with contrast performed for staging purpose.50.4 Gy dose of radiotherapy was delivered in 28 fractions at rate of 1.8 Gy per fraction in two phases. In phase I we delivered external beam radiotherapy through 02 fields anterior & posterior up to 36 Gy, with 05 cm proximal & distal margins to tumor and 03 cm transverse margins for nodal coverage for achieving 95% dose delivery at planning target volume. In phase II external beam radiotherapy was delivered through 03 fields one anterior & two posterior oblique fields with adequate coverage of tumor target volumes through sparing organ at risk i-e lungs, spinal cord & heart to prevent from radiotherapy induced injuries to these critical organs. Inj cisplatin 75 mg/m2 IV D1 of week 1^{st}, 5^{th},8^{th} & 11^{th} and Inj 5 Flurouracil 1000mg/m2 24 hours IV infusion during 1^{st}, 5^{th}, 8^{th} & 11^{th} weeks were infused. The nutritional support was assessed in all patients by calculating per day calories requirements. Nutritional supplements were given oral, parenteral routes routinely in our ward. Patients who presented with absolute dysphagia were planned for feeding gastrostomy & self expandible metallic esophageal stent.CBC was performed on weekly basis for evaluation of neutropenia during definitive chemo radiation and during two cycle of adjuvant chemotherapy infused. Neutropenia grading was assessed according to basis of common Terminology Criteria for Adverse Events (CTCAE).The data was statistically analyzed.

RESULTS:

Sixty two patients of locally advanced esophageal cancer included in study**.** Most of the patients were above 40 year of age. The average age of patients and duration of disease the was 46.45±10.59 years (95%CI: 46.45±10.59) and 3.5±1.17 months (95%CI: 3.20 to 3.80) respectively as presented in table I.

27(43.5%) were male and 35(56.5%) were female figure1. Dysphagia was the commonest clinical presentation i.e. 37(59.7%) followed by vomiting in 18(29%) and weight loss in 7(11.3%) cases. Stage III-C 34%, stage IIIB 26% and stage IIB 17% was found in patients table II, figure II. Neutropenia was assessed on weekly basis on CBC. Neutropenia grading was Neutropenia grading from grade 1 to 4 were 2%, 34%, 48%,16% cases respectively according to common Terminology Criteria for Adverse Events (CTCAE) presented figure III.

Table I. Descriptive Statistics of Patients(n=62)

Statistics	Age (Years)	Duration of Disease (months)
Mean ± SD	46.45±10.59	3.5±1.17
95% Confidence Interval	43.76 to 49.14	3.20 to 3.80
Median (IQR)	48.5(16)	3.5(1)
Maximum	62	7
Minimum	25	2

Table II. Stage of Disease (n=62)

Stage	Percentage
Stage IIB	17%
Stage IIIA	23%
Stage IIIB	26%
Stage IIIC	34%

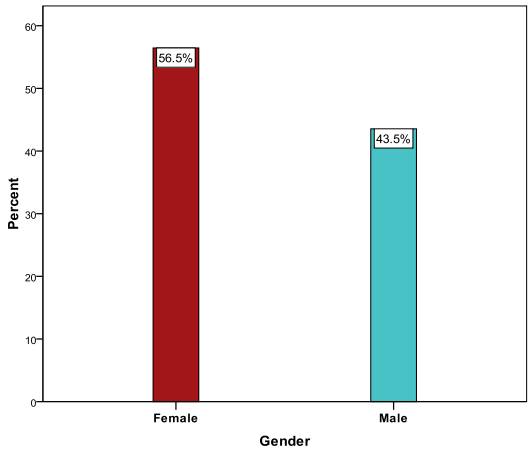

Figure -1.Gender Distribution (n=62)

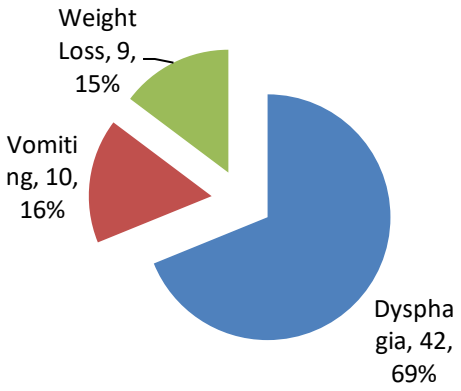

Figure II:Clinical Presentations(n=62)

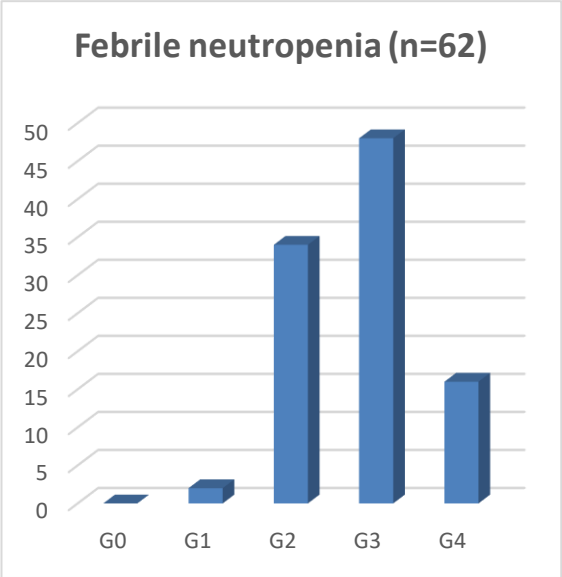

Figure III.Grading of febrile neutropenia(n=62)

DISCUSSION:

Neutropenia is most common life threatening oncological emergency. Neutropenia is common cause of caner chemotherapy related mortality and morbidity. Neuropenia imposes economic burden on health care resourrces and source of anxiety and stress for treating physicians and patients. In cancer patients there is alteration in cell mediated and humoral immunity defense mechanisms. And these sequele of neoplastic lesion itself or related to treatment offered to patients in form of chemotherapy and radiotherapy.Anti neoplatic drugs target rapidly dividing cells of body that includes bone marrow cells,germinal layer of dermis & epithelia of gastro intestinal tract.Severity of neutropenia depends upon dose,duration and infusional timiming of chemotherapy infusion.Frequency of febrile neutropenia also increase when radiotherapy is combined with chemotherapy(concurrent chemoradiation).Neutropenia grading also depends upon type of radiation,dose per fraction,duration and radiotherapy field sites &sizes.Neutrophil count usually begin to decrease three to seven days after chemotherapy and achieve nadir level usually seven to ten days after infusion of chemotherapy.Neutropenia is diagnosed on CBC and graded according absolute neutrophil count(ANC).Neutropenic patients usually presents in OPD and emergency department with complain of fever,rigors,oral ulcers,sore throat,cough,diarrhea,hypotension,tachyca rdia, tachypenea,skin lesions and focus of infection on intravenous cannula,central venous access device and perianal area.In extreme conditions changes in mental status such as confusion or even loss of consciousness.Neutropenia management is based upon grade of neutropenia,general condition of patient includes performance status of cancer patient and underlying risk factors.

In neutropenic patients preventive measurses that include use of gowns,gloves,face masks by health care providers,strict attention to hand washing must be implemented.Cancer patients should avoid from large crowds,avoid consumption of undercoocked meat,fish,raw eggs,avoid from handling pets birds and animals.Female patients should use sanitary napkins instead of tampons.In febrile neutropenic patients broad spectrum antibiotics is recommended even infection source is not obvious.[18]Prophylaxis use of granulocyte colony stimulating factor(G-CSF) is recommended for patients who have high risk features for developing neutropenia,include old age, siginificant co morbid,poor performance status, poor nutritional status and 20 percent or more

myelosuppresion on chemotherapy drugs.[19]

Cancer chemotherapy induced neutropenia in 06 to 50% of patients depend upon type of malignancy,tumor stage,patient performance status and chemotherapy regimen.[19]So identification of these high factors are very essential for justifiable use of granulocyte colony stimulating factors(G-CSF).In Granulocyte colony stimulating guidelines taxene based,platinum based chemotherapy regimens were not classified as high risk regimens for developing neutropenia.[20,21]Prophyactic use of granulocyte stimulating factor(G-CSF) improves patients quality of life and reduced prolonged hospitilization.[22,23]

In our study chemotherapy induced neutropenia was most common in elderly patients with poor performance status,poor nutritional status and advanced stage.Majority of patients has developed neutropenia grade III &IV.Neutropenia was less in patients of young age,good performance status and adequate nutritional intake and support.Our study results were similar to study of Wakui-R,et al for definitive chemo radiotherapy for elderly patients.[24]In our study three patients expired due to neutropenia grade IV.Three patients refused second cycle of chemotherapy due to development of neutropenia grade III and vomiting grade III. Five patients had finacial problems and discontinue chemotherapy and received radical dose of radiotherapy 50.4Gy as per protocol.Chemo radiation was completed in fifty one patients as per decised protocol.In locally advanced esophageal cancer literature review showed neutropenia grade III range from 11% to 50% of patients which is similar to our study.[25,26,27]our study is single institute based study with small number of patients,so further studies with suffient sample size and with long term surveillance is required.

CONCLUSION:

Chemotherapy induced neutropenia is most common oncological emergency. It increases morbidity and mortality if not assessed timely during cancer treatment**.**

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