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Original Research Article

The Role of Haematological and Inflammatory Parameters in Patients with Oral Cancer against Chemotherapies: Cisplatin with 5-Flurouracil and Cisplatin with Capecitabine

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Conflict of interest: Nil

Abstract:

Background: Anemia is reported by many studies as an important risk factor for poor locoregional disease control and survival in head and neck carcinoma.

Aim and Objective: The objective of this study was to evaluate the benefits of concurrent capecitabine and cisplatin over concurrent cisplatin and 5-FU in locally advanced squamous cell oral cancer by investigating the relationships among serum CRP level, IL-6, TNFα, and Hb, HCT, Ferritin, Transferrin, EPO prognosis in oral cancer patients.

Material and Methods: Total 152 Histological proven eligible cases of locally advanced stage (III, IV, M0) head and neck cancer patients attending our radiotherapy O.P.D in year 2016-2018 were enrolled in the study. Blood samples were obtained at 8:30 a.m. after overnight fasting and subsequently routine analyses of Hb, HCT, CRP, IL-6, IL-1β, TNFα, EPO serum iron, transferrin, and ferritin were performed by Autoanalyzer & commercially available enzyme-linked immunosorbent assays (ELISA). The enrolled patients in this study who were to receive concurrent chemo radiotherapy following 2 cycles of Neoadjuvant taxol and cisplatin chemotherapy of whom 74 patients were randomized in Arm-I where cisplatin(75mg/m^2 in day1 and day2) and 5-FU(750mg/m^2 in day1,2,3) was given from the first day of radiotherapy at interval of 3-weeks, total five cycles were given, and 78 patients were in Arm II where cisplatin (75mg/m2 in day1 and day2) and capecitabine (750mg/m^2 in two divided doses from day1-14,with pyridoxine 100 mg bd was given on days 1–14) was given from the first day of radiotherapy at interval of 3-weeks, total five cycles were given.

Results: The age ranges were, Arm1- Male-32-71 Years, Female-38-73 Years, Arm 2-Male-34-73Years & Female-42-68 Years. The cohort had more male patients, Arm1-62/74 (83.78%); Arm2-69/78 (88.46%). Predominance of T3 in Arm1-32/74 (43.24%), Arm2-36/78(46.15%) patients, and Overall Stages in Arm1-StgIII-35/74(47.29.%), Arm2-StgIII-37/78(47.43%) and for Stage IV- Arm1-39/74 (52.70%); Arm2-41/78(52.56.%) patients. It was found that the haemoglobin levels (mg/dl, mean) of all treatment cycles and follow up were Arm1-11.260,10.212,11.301, 10.983, 11.250, 12.431; Arm2-10.313, 9.452, 9.432, 10.201, 10.511, 11.103 and significantly inversely correlated with CRP, IL6, TNFα, IL-1β($P<0.05$). The treatment response in two treated groups, was found slightly higher in the patients treated with Cisplatin + 5Fu and subsequently EPO levels were higher in patients treated with Cisplatin + 5Fu than in Arm2-Cisplatin + Capecitabine treated group.

Conclusion: A low hemoglobin value in a cancer patient could be itself indicating a poor general condition of the patient, since hypoxia may be an expression of tumor aggressiveness. Similarly elevated Tnfα and IL6 could be indicated a poor general condition of the patients. In conclusion, concurrent chemoradiotherapy with capecitabine and cisplatin was found to be well tolerated and effective in patients with locally advanced head and neck cancer. Accordingly, this regimen can be regarded as an important chemoradiotherapy option for advanced head and neck cancer, although long-term follow-up is needed to evaluate the late treatment failure and complications.

Keywords: Hb, inflammatory markers, Capecitabine; Chemotherapy; Cisplatin; oral cancer.

Introduction

Chemotherapy or radiotherapy may be worsened by activation of the immune system with release of inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ),

and interleukins (IL)-1, -6, -8 and -10[1,2]. These inflammatory mediators cause anemia via a variety of pathophysiological mechanisms: decreased red cell half-life due to dyserythropoiesis with red cell damage and increased erythrophagocytosis (TNF-α); inadequate erythropoietin (EPO) response for the severity of anemia; impaired responsiveness of erythroid cells to EPO (IFN-γ, IL-1, and TNF-α);inhibited proliferation and differentiation of erythroid cells (IFN-γ, IL-1, TNF-α, and α-1-antitrypsin) and pathologic iron homeostasis due to increased divalent metal transport 1 (IFN-γ) and transferrin receptor expression (IL-10) in macrophages, reduced ferroportin 1 expression (IFN-γ and IL-6-induced high hepcidin levels) in enterocytes and macrophages, and increased ferritin synthesis (TNF-α, IL-1, IL-6, IL-10)[3,4].

The pro-inflammatory cytokines also induce changes in the proliferation of erythroid progenitors, erythropoietin (EPO) production, and survival of circulating erythrocytes. This inflammatory state is characterized by elevated plasma C-reactive protein (CRP) levels, weight loss with hypoalbuminemia, and erythropoietin-resistant anemia. Plasma CRP levels reflect the levels of interleukin (IL)-6, which also modulates the concentration and biological activity of hepcidin, and other acute-phase proteins that may induce serious hematologic, nutritional, and metabolic disorders[5].

The prevalence of anaemia in patients with cancer is remarkably high. In the "European Cancer Anaemia Survey"(ECAS) 39% of cancer patients were anaemic at baseline when they were included in the survey. In those receiving chemotherapy incidence of anaemia was noted in 67% of patients at some point during a 6 month surveillance phase (anaemia was defined as haemoglobin (Hb)<12 g/dl). Similar data have subsequently been obtained in a survey conducted in Austria. Anaemia was correlated with low performance status and many patients did not receive anaemia therapy [6].

Iron is an essential cofactor for various enzyme systems which can be classified into heme and non-heme proteins. About two third of the body's total iron content of 4–5 g is bound to heme-proteins, mainly hemoglobin and myoglobin. Plasma iron levels are regulated by the glycoprotein, transferrin which has two high affinity binding sites for trivalent iron. Transferrin, as the main iron transport protein, supplies iron to iron-dependent systems. The uptake of iron into cells is affected by the transferrin receptor (TfR1). By binding to transferrin, iron becomes soluble in plasma, and the synthesis of free oxygen radicals by free trivalent iron is tightly limited. Normally, the iron-saturation of transferrin (TSAT) lies around 30%; a TSAT below 20% points to iron deficiency, a TSAT over 45% to iron overload. Above a TSAT of 60%, free, nontransferrin-bound iron is released into plasma and damage of parenchymal cells can occur [7]. Hence, the etiology of cancer related anemia is often multifactorial, including effects of the disease process itself (e.g. bleeding) or its treatment, whether it is chemotherapy or radiotherapy. Factors associated with anemia are disorders of iron metabolism, reduced number of erythroid progenitor cells, increased levels of inflammatory cytokines, extra corpuscular haemolysis, catabolism of patients with tumor burden and relative deficiency of erythropoietin[8].

Capecitabine is an oral fluoropyrimidine agent used as single agent in breast and gastrointestinal cancer patients. Combination of cisplatin with 5-FU has shown synergistic effect in prior study [9,10], but the clinical effect of cisplatin is not clearly analyzed in oral cancer compared to gastrointestinal cancer. The adverse effects of 5-FU, such as oral mucositis, which is an additive complication to radiation, or bone-marrow suppression, can result in treatment- related hospitalization or mortality, thereby compromising the quality of life and compliance to treatment, oral capecitabine which mimics continuous 5-FU infusion, has substantial activity in squamous cell carcinoma of head and neck and is replacing 5-FU in many solid tumors as well as in advanced head and neck squamous cell carcinoma[11,12].

Previous studies have shown the clinical efficacy of capecitabine and cisplatin (XP) combination regimen in unselected metastatic breast cancer (MBC) patients, but with different patient population and different dosage, schedule of chemotherapeutic agents [13].

A study also showed that capecitabine/cisplatin therapy was a feasible method for the treatment of patients with advanced Biliary Tract Cancer (BTC), and also suggested that the CA19-9 response may be a surrogate biomarker for patients with BTC who were treated with capecitabine/cisplatin [14]. It was also reported in a study that the cisplatin combined with capecitabine induced chemotherapy for local nasopharyngeal carcinoma(NPC) could improve the quality of life and reduced toxic and side effects[15].

A phase 3 randomized clinical trial documented that the induction chemotherapy (IC) with 2cycles of paclitaxel, cisplatin, and capecitabine (TPC) for patients with stage IVA to IVB nasopharyngeal carcinoma (NPC) improved failure-free survival (FFS) compared with 2 cycles of cisplatin and fluorouracil (PF) , with no increased in toxicity profiles[16].

The observed response rate and time to progression (TTP) in XP combination chemotherapy showed modest antitumor efficacy in patients with metastatic HCC as systemic first-line treatment in a

study and subsequently suggested, XP combination chemotherapy was having tolerable toxicity and favourable overall survival (OS) time [17].
Considering the toxicity of cisplatin in heavily pre-treated patients, there were relatively scared reports about combining cisplatin to capecitabine in breast, gastric, colon cancer[18], more advanced studies in combination with different biomarkers particularly haematology and inflammatory markers are required for proper evaluation of combined chemotherapies [19]. The treatment strategies of Cisplatin with 5-flurouracil and Cisplatin with Capecitabine are undefined in oral cancer against inflammatory and haematological levels responses. C-reactive protein (CRP) is a predominant protein of the acute phase response; its blood levels have long been used as a minimally invasive index of any ongoing inflammatory response, including that occurring in cancer [20].

It has been documented that the elevated serum CRP was associated with poor overall survival, subsequently elevated conventional CRP was associated with progressive disease and advanced disease stages, subsequently it was also suggested that the CRP blood levels (which only measure the soluble pentameric isoform) should be interpreted as a diagnostic index of tissue health and homeostasis rather than its diagnostic significance in assessing disease progression or remission [21].

The Baseline levels of CRP in health, in controlled disease or in disease remission have also been documented in cancer patients, will be < 10 mg/ml. Levels closer to 1–3 mg/ml are better indicators of good health and control of disease [22]. The production of CRP is affected by inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1 (IL-1) and tumour necrosis factor (TNF)-alpha, which are secreted by monocytes or macrophages due to inflammation or cancer. Especially, interleukin-6 is one of the multifunctional cytokines that control humoral immunity and are involved in inflammation, infection responses, and metabolic regulation [23].

Serum concentrations of IL-6 and CRP are positively correlated. A recent study suggested that IL-6 also affected cancer cell biology [2]. It has been confirmed that an IL-6 signalling pathway stimulates cancer progression through the IL-6 receptor on the cancer cell surface in oral, prostate cancer [24]. A study also revealed that the IL-6 signalling system in human oral squamous cell carcinoma may be involved in the development of cancer by controlling angiogenesis and lymphangiogenesis [25]. Other inflammatory cytokines, such as IL-1 and TNF-alpha, were also related to the immune-expression increases in cancer patients [26,27].

It has also been documented that the normocytic anemia was the most prevalent form of anemia at the time of oral cancer diagnosis, and moderate to severely low hemoglobin levels (OR 3.94; 95%IC 1.23-12.64), model 1 (OR 6.46; 95%CI 1.18–35.24) were associated with the diagnosed presence of OSCC, albeit data were missing on hematological examinations [28]. A study results supported the positive prognostic effect of Hb level > 12 g/dl and >13 g/dl before radiation therapy and/or chemoradiotherapy on response to treatment and overall survival but not the disease-free survival [29]. It was also reported that the level of Hb having a significant effect on treatment outcome was at 10.7 g/dl. In addition to pretreatment Hb levels > 10.7 g/dL, and also observed that improved locoregional control (LRC) in Stage III/IVA HNSCC were significantly associated with better performance status, lesser grade of mucositis and no interruptions or interruptions less than five days during radiotherapy[30].

The diagnosis of anemia was based on the World Health Organization standardized cut-off values of Hb < 13 g/dL and Hct< 39% for men, and Hb< 12 g/dL and Hct< 36% for women. The type of anemia was classified by mean corpuscular volume (MCV) as microcytic (MCV < 80 fL), normocytic (MCV = 80–100 fL), or macrocytic (MCV >100 fL). Severity of anemia was classified according to the Hb level as mild (11–11.9 g/dL for women, 11–12.9 g/dL for men) or moderate to severe (< 10.9 g/dL). For analysis and comparison purposes, Hb values within the normal range were classified as “no anemia [31].

A study indicated that, cisplatin combined with capecitabine was safe and effective. This may also cause the concentration of capecitabine in tumor cells which was much higher than that in normal cells, so it was high anti-tumor activity and low toxicity [32].

A previous pilot study has also evaluated the feasibility of definitive CRT with capecitabine and cisplatin for oesophageal cancer and subsequently suggested that, esophagitis was the common adverse effect which was observed, with a grade 3 or 4 intensity in 27.8% of the patients, but the concurrent chemoradiotherapy with capecitabine and cisplatin was found to be well-tolerated and seemed to be effective in patients with oesophageal cancer [33].

A randomized study has also been documented that the incidence of grade 3 or 4 esophagitis in concurrent chemoradiotherapy with 5-FU and cisplatin was 20.0%, which was higher than with radiotherapy only (4.8%). The incidence of esophagitis was not so different between chemoradiotherapy with capecitabine/cisplatin and

5-FU/cisplatin, but suggested that capecitabine based treatments were associated with superior RR and OS than infusional 5-FU regimens [34,35]. A study of comparable efficacy which compared to 5-FU/cisplatin and suggested that, it was mostly associated with decreased toxicity and increased ease of administration [36]. A study reported that the resistance to cisplatin remains a major challenge that hindered the success of OSCC treatment. Recently, new factors such as epigenetic, biological /biochemical processes and tumor microenvironment have also received increasing attention in the study of the mechanisms of chemo resistance in OSCC, subsequently the combination therapies of natural products and traditional anticancer drugs have shown potential on improving therapeutic effect [37]. In view of above facts a study with complete haematological and inflammatory markers are needed to evaluate the role of biochemical and haematological parameters against combined treatment of capecitabine compared to 5-FU with cisplatin in oral cancer. Hence, the objective of this study was to evaluate the benefits of concurrent capecitabine and cisplatin over concurrent cisplatin and 5-FU in locally advanced squamous cell oral cancer by investigating the relationships among serum CRP level, IL-6, TNFα, and Hb, HCT, Ferritin, Transferrin, EPO prognosis in oral cancer patients.

Material and Methods:

Study Site: Department of Radiotherapy, King George's Medical University, Lucknow, Uttar Pradesh, India.

Study Design: Comparative and prospective study.

Sample Size: 152 of both sexes

Study Group: Two Groups: Arm-I: 74 patients were in Arm-I where cisplatin (75mg/m^2 in day1 and day2) and 5-FU (750mg/m^2 in day1,2,3) was given from the first day of radiotherapy at interval of 3-weeks, total five cycles were given.

Arm-II : 78 patients were in Arm II where cisplatin (75mg/m2 in day1 and day2) and capecitabine (750mg/m^2 in two divided doses from day1-14,with pyridoxine 100 mg b.d was given on days 1–14) was given from the first day of radiotherapy at interval of 3-weeks, total five cycles were given.

Inclusion Criteria:

- Histologically proven patients of head and neck cancer of locally advanced stage (III, IV, M0).
- Patients who have not received previous definitive treatment (surgery chemotherapy, radiotherapy etc.) for the malignant disease in last 5 years.

The patients were considered anaemic if pre-RT/CRT hemoglobin was <11.5 g/dl in females and <12 g/dl in males according to the WHO criteria for anemia [30]. Acute toxicity during radiotherapy was graded according to the RTOG radiation toxicity criteria. Patients in apparently good general condition and able to tolerate the treatment (Grade 0 and 1 WHO Performance Status) Plus, adequate haematological (WBC count $\geq 4 \times 10^9$ l^{-1}, platelet count $\geq 100 \times 10^9$ l^{-1}, haemoglobin ≥ 9 g dl^{-1}), renal (serum creatinine ≤ 1.5 mg dl^{-1} and creatinine clearance $\geq$ 50 ml min^{-1}), and hepatic (total bilirubin ≤ 2.0 mg dl^{-1} and serum transaminase level ≤ 3 times the upper limit of the normal range) levels were also required.

A total 152 Histological proven eligible cases of locally advanced stage (III, IV, M0) head and neck cancer patients attending our radiotherapy O.P.D in year 2016-2018 were enrolled in the study (Table-1 & Table -2 in details).

Table 1: Details of Patients and Treatment Arms (Groups): Arm-I (Cisplatin & 5 FU); Arm-II (Cisplatin & Capecitabine)

Characteristic	Treatment Arms (groups)		Total Patients
Eligible patients	Arm-I (Cisplatin+5Fu)	Arm-II (Cisplatin+Capecitabine)	152
	74	78	
Patients absconded before treatment	2	3	5
Patients absconded during treatment	5	4	9
Analyzable Patients	67	71	138

Table 2: Details of Patients Characteristic

Characteristic	Arm I No. (%)	Arm II No. (%)
Age (yrs) Range	M-32-71; F-38-73	M-34-73; F-42-68
Sex (M-Male; F- Female)	M-62; F -12	M-69; F-9
W.H.O performance status		
Grade-0	49, (66.21%)	52, (66.66%)
Grade-1	25, (33.78%)	26, (33.33%)
Site of primary tumour		
Lip	2, (2.70%)	3, (3.86%)
Oral tongue	6, (8.10%)	4, (5.12%)
Floor of mouth	5, (6.75%)	7, (8.97%)
Hard palate	13, (17.56%)	18, (23.07%)
Alveolus	25, (33.78%)	27, (34.61%)
Retromolar trigone	8, (10.81%)	7, (8.97%)
Buccal mucosa	15, (20.27%)	12, (15.38%)
pathology		
Sq.cellca.well differentiated	23, (31.08%)	21, (26.92%)
Sq.cell ca mod.differentiated	48, (64.86%)	52, (66.66%)
Sq cell ca.poorly differentiated	1, (1.35%)	2, (2.56%)
Sq cell ca.undifferentiated	nil	nil
Anaplastic ca	nil	nil
Adenosquamous carcinoma	1, (1.35%)	1, (1.28%)
adenocarcinoma	nil	nil
unspecified	1, (1.35%)	2, (2.56%)
T stage (1992 AJCC)		
T1	9 (12.16%)	8 (10.25%)
T2	19 (25.67%)	22(28.20%)
T3	32 (43.24%)	36(46.15%)
T4a	14 (18.91%)	12(15.38%)
N stage (1992 AJCC)		
N0	8, (10.81%)	6, (7.69%)
N1	23, (31.08%)	25, (32.05%)
N2	36, (48.64%)	39, (50%)
N3	7, (9.45%)	8, (10.25%)
Overall stage (1992 AJCC)		
III	35(47.29%)	37, (47.43%)
IV	39 (50.70%)	41, (52.56%)

Laboratory assays: Blood samples were obtained at 8:30 a.m. after overnight fasting and subsequently routine analysis of Hb, HCT, CRP, IL-6, IL-1β, TNFα, EPO serum iron, transferrin, and ferritin were performed by Autoanalyzer& commercially available enzyme-linked immunosorbent assays (ELISA). Pre-therapeutic CRP levels and hemoglobin concentration were measured in peripheral venous blood samples. Anemia was defined as hemoglobin concentration<11 g/dl, known as a predictor of tumor hypoxia [17].

The normal serum level of CRP was defined as 0.3mg/dL or lower, according to several references [18,19]. Comparisons between two groups were calculated with chi-square or fisher exact test for qualitative data. For prognosis analysis, we examined the factors of the primary site, age, gender, KPS, smoking history, current smoking status, clinical stages, anemia, pre-therapeutic CRP level and radiation treatment modalities.

Real-Time polymerase chain reaction (RT-PCR): Total RNA of the experimental groups, OSCC cells was extracted using the TRIzol reagent (Ambion, USA). RNA was reverse-transcribed into cDNA with a one-step RT-PCR kit (TIANGEN Biotech Co., Ltd. Beijing China) at 37°C for 60 min. Real-time quantitative PCR, using Real Master Mix (SYBR Green) (Tiangen) with a 7800 ABI RTPCR System (Applied Biosystems, Foster City, CA, USA). PCR proceeded under the conditions of 95°C for 30 s, 95°C for 15 s, 60°C for 30 s, and 68°C for 30 s (40 cycles). The relative gene expression was calculated using the 2(–

DDCT) method in at least 3 independent experiments. The resultant mRNA was normalized to its own B-actin. The reported primers were used for the RTPCR [16]

Study Treatment: Total 152 Patients enrolled in this study who were to receive concurrent chemoradiotherapy following 2 cycles of Neoadjuvant taxol and cisplatin chemotherapy of whom 74 patients were randomized in Arm-I where cisplatin(75mg/m^2 in day1 and day2) and 5-FU(750mg/m^2 in day1,2,3) was given from the first day of radiotherapy at interval of 3-weeks, total five cycles were given, and 78 patients were in Arm II where cisplatin(75mg/m^2 in day1 and day2) and capecitabine(750mg/m^2 in two divided doses from day1-14,with pyridoxine 100 mg b.d was given on days 1–14) was given from the first day of radiotherapy at interval of 3-weeks, total five cycles were given.

Radiotherapy was given by External beam Conventional Method (200CGy/fraction to a total dose of 70Gy in 35 fractions in 7-weeks by cobalt60 to primary tumor site and neck along with concurrent chemotherapy of respective arms from the first day of radiotherapy.

All the patients underwent complete dental evaluation and treatment before initiation of radiotherapy. Patients were evaluated 8 weeks from completion of treatment. End point was to evaluate clinical benefits of concurrent chemoradiotherapy with capecitabine and cisplatin on response rate and its corelation with Hb, HCT, EPO, TNFα, IL6, CRP etc (Haematology & Inflammatory Biochemical Markers).

Study Assessments: Before starting treatment, all patients underwent a full medical history and physical examination, blood tests, computed tomography (CT) or magnetic resonance imaging of the head and neck, and chest X-ray /CT-scan of the chest if low neck nodes were involved).

Assessment of tumor response was done by clinical examination, investigations (X-rays, CT-scan) 4-6 weeks after completion of treatment. Biopsy or fine needle aspiration cytology to determine pathological response was not performed routinely; it was done only in case of partial response/suspected lesion to confirm the presence of disease. The definition of complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) was based on the standard definitions established by WHO (1979).

Results

A total of 152 patients pathologically diagnosed with oral cancer were included in the study. The age ranges were, Arm1- Male-32-71 Years, Female-38-73 Years, Arm 2-Male-34-73Years & Female-42-68 Years. The cohort had more male patients, Arm1-62/74 (83.78%); Arm2-69/78 (88.46%). Predominance of T3 in Arm1-32/74 (43.24%), Arm2-36/78(46.15%) patients, and Overall Stages in Arm1- StgIII-35/74(47.29.%), Arm2-StgIII-37/78(47.43%) and for Stage IV-Arm1-39/74 (52.70%); Arm2-41/78(52.56.%) patients. The levels of serum CRP, IL-6, IL1β and TNF-alpha as well as Haemoglobin (HB), HCT, S. Iron, EPO, S. Ferritin and S. Transferrin in patients with oral cancer, treated by Arm1- Cisplatin & 5Fu; Arm 2- Cisplatin & Capecitabine were shown in Table-4. The baseline parameters of inflammatory and haematological biomarkers of two treatment groups are almost similar as the patients were under correction measure before chemotherapy. It was found that the haemoglobin levels (mg/dl, mean) of all treatment cycles and follow up were Arm1-11.260,10.212,11.301, 10.983, 11.250, 12.431; Arm2-10.313, 9.452, 9.432, 10.201, 10.511, 11.103 and significantly inversely correlated with CRP, IL6, TNFα, IL-1β($P<0.05$). Figure-1 and Figure-2 showed the inverse correlation with CRP, IL6, TNFα, IL-1β levels against HB levels in two treated groups at different treatment cycles and follow up in oral cancer patients. Subsequently Figure-3 and Figure-4 also showed positive correlation with HB levels against Serum Iron, Serum Ferritin and Serum Transferrin. Patients of both treated groups at Cycle IV had a significant difference in all inflammatory as well as Haematological parameters as compared to baseline and 2nd follow up. The treatment group-Arm1-Cisplatin + 5Fu showed the significantly ($P<0.05$) higher HB levels and lower CRP, IL6, TNFα , IL1β levels as compared to Treatment Group Arm2-Cisplatin + Capecitabine in the patients at the stage of 2nd follow-up, but acute toxicity were significantly higher($P<0.05$) in the patients treated with Cisplatin + 5Fu.

Table-3 also showed the treatment response in two treated groups, was found higher in the patients treated with Cisplatin + 5Fu and subsequently EPO levels were significantly higher in patients treated with Cisplatin + 5Fu than in Arm2-Cisplatin + Capecitabine treated group.

It was also found that advanced stage patients had significantly lower Hb concentrations compared with early stage. we found that CRP, IL-6, TNFα, IL-1β, ferritin, EPO were significantly higher in the stage III-IV patients than in the stage I-II patients. In contrast, iron was significantly lower in stage III-IV patients ($P<0.05$).

RT-PCR Strong signals of both TNF-α and IL-6 were detected in most of the examined tumor samples (Fig-5) TNF-α mRNA levels were elevated nearly 4–7 fold in OSCC tissues of both the groups compared to the levels of NC ($P<0.05$). IL-6mRNA levels were similarly elevated 3–6 fold in OSCC tissues of both the groups ($P<0.05$).

Table 3: Treatment response in two groups (Arm-1, Cis+ 5Fu; Arm-2, Cis+ Capecitabine)

Variables	TNCR	TCR	NCR	PR	NR	EP
Arm-1	46	38	32	22	3	3
Arm-2	37	31	25	28	6	7

TNCR-Primary Tumor & Neck Node Complete Response; TCR-Primary Tumor Complete Response; NCR-Secondary Neck Node Complete Response; PR- Partial Response; NR- No Response, EP- Epsconded.

Table 4: Haematological and Inflammatory Biochemical Parameters in Two Treated Groups (Arm-1, Cis+ 5Fu; Arm-2, Cis+ Capecitabine)

Groups/ Variables	Baseline	1st Cycle	2nd Cycle	3rd Cycle	4th Cycle	FU-1st Month	FU-2nd Month
Hb mg/dl							
Arm1	12.320±1.54	11.260±1.70	10.212±0.76	11.301±1.78	10.983±2.76	11.250±1.90	12.431±1.56
Arm2	12.054±1.79	10.313±2.87	9.452±3.76	9.432±2.10	10.201±2.91	10.511±1.65	11.103±2.09
CRPµg/ml							
Amr1	18.201±2.11	30.765±1.65	31.321±3.78	28.013±1.79	25.865±3.98	14.654±1.98	9.560±1.21
Arm2	18.534±3.20	30.765±2.00	30.310±3.21	28.013±2.11	27.863±4.12	14.012±1.32	10.650±1.45
TNFα pg/ml							
Arm1	25.983±4.32	33.569±5.34	32.563±3.78	26.897±2.13	22.753±2.65	19.243±1.89	18.662±2.21
Arm2	28.958±3.98	34.012±4.87	33.761±4.11	28.013±2.89	25.756±3.11	23.510±1.76	22.432±1.98
IL6 pg/ml							
Arm1	21.345±1.54	23.435±1.98	19.321±2.32	18.564±2.15	17.543±1.09	16.984±1.75	16.210±2.11
Arm2	22.567±2.10	23.987±1.76	21.543±2.65	20.765±1.97	18.439±1.47	17.654±1.34	17.043±2.23
IL-1βpg/ml							
Arm1	30.210±5.675	31.453±3.943	29.564±4.672	28.564±4.789	26.543±5.671	25.569±3.201	25.103±2.993
Arm2	30.985±4.321	31.875±4.561	30.654±5.432	30.103±4.102	29.987±6.345	28.675±2.987	26.899±4.876
EPO pg/dl							
Arm1	20.432±2.89	30.564±3.65	27.543±2.39	26.547±1.56	25.874±2.78	24.349±1.76	23.983±2.80
Arm2	21.105±3.11	30.987±2.98	28.430±3.43	27.455±2.03	27.654±1.95	26.129±3.12	25.997±2.98
Ferritin µg/dl							
Arm1	302.435±35.17	334.543±30.45	280.564±28.98	279.204±32.78	263.871±33.78	243.657±36.76	240.876±35.65
Arm2	301.987±36.98	339.765±34.98	281.769±31.65	282.653±35.43	280.768±36.92	268.967±35.87	249.675±34.93
Transferrin µg/dl							
Arm1	221.432±30.98	215.986±29.87	216.567±30.74	218.789±24.78	221.852±31.65	221.987±27.58	224.875±30.45
Arm2	220.983±34.56	218.543±32.76	212.675±29.12	216.587±26.92	219.432±29.98	222.764±29.12	223.285±31.32
S.Iron mg/dl							
Arm1	51.546±5.74	50.765±4.67	47.789±6.23	48.102±3.98	48.671±5.71	56.789±6.22	57.342±3.86
Arm2	51.561±4.87	49.432±5.12	45.872±4.33	46.783±4.10	46.987±5.93	51.789±5.71	54.768±3.54

Table 5: Details of Acute Toxicity in patients of Two Treated Groups, Arm-I (Cisplatin & 5 FU); Arm-2 (Cisplatin & Capecitabine)

ARM I	acute toxicity N=64	N=67	cisplatin+5FU			
	Grade (% of patients)					
		Grades				
Haematological		1	2	3	4	3/4(%)
Anaemia		17/67(25.3%)	13/67(19.4%)	16/67(23.8%)	14/67(20.8%)	1%
Leukopenia		37/67(55.2%)	36/67(53.7%)	21/67(31.3%)	17/67(25.4%)	1.23%
Neutropenia		22/67(32.8%)	14/67(20.8%)	11/67(16.4%)	7/67(10.4%)	1.60%
Thrombocytopenia		15/67(22.4%)	14/67(20.9%)	11/67(16.4%)	8/67(11.9%)	1.40%
Febrile neutropenia		7/67(10.4%)	5/67(7.5%)	4/67(5.9%)	nil	(%)
Nonhaematological						
Nausea		33/67(49.3%)	32/67(47.7%)	7/67(10.4%)	3/67(4.5%)	2.30%
Vomiting		31/67(46.3%)	32/67(47.7%)	4/67(5.9%)	3/67(4.5%)	1.30%
Renal dysfunction		12/67(17.9%)	3/67(4.5%)	4/67(5.9%)	nil	
Mucositis		14/67(20.9%)	33/67(49.3%)	29/67(43.4%)	18/67(26.8%)	1.60%
Dermatitis (in field)		36/67(53.7%)	24/67(35.8%)	4/67(5.9%)	2/67(2.9%)	2%

Diarrhoea		7/67(10.4%)	6/67(8.9%)	3/67(4.5%)	2/67(2.9%)	1.50%
Hand-foot syn-drome		3/67 (4.47%)	3/67(4.47%)	1/67 (0.67%)	2/67 (1.34%)	0.50%
ARM II	**acute toxicity N=71**		**cisplatin+capecitabine**			
	Grade (% of patients)					
		Grades				
Haematological		1	2	3	4	3/4(%)
Anaemia		20/71(28.2%)	8/71(11.3%)	3/71(4.2%)	2/71(2.8%)	1.50%
Leukopenia		10/71(14.1%)	14/71(19.7%)	4/71(5.6%)	2/71(2.8%)	2.00%
Neutropenia		10/71(14.1%)	11/71(15.5%)	2/71(2.8%)	1/71(1.4%)	2%
Thrombocytopenia		21/71(29.6%)	3/71(4.2%)	2/71(2.8%)	nil	(%)
Febrile neutropenia		1/71(1.4%)	2/71(2.8%)	1/71(1.4%)	nil	(%)
Nonhaematological						
Nausea		39/71(54.9%)	29/71(40.8%)	4/71(5.6%)	3/71(4.2%)	
Vomiting		25/71(35.2%)	36/71(50.7%)	6/71(8.5%)	nil	
Mucositis		14/71(19.7%)	30/71(40.3%)	32/71(45%)	19/71(26.7%)	
Dermatitis(in field)		11/71(15.5%)	29/71(40.8%)	5/71(7%)	2/71(2.8%)	
Renal dysfunction		11/71(15.5%)	2/71(2.8%)	1/71(1.4%)	nil	
Diarrhoea		7/71(9.8%)	5/71(7%)	3/71(4.2%)	nil	
Hand-foot syn-drome		4/71(5.6%)	3/71(4.2%)	nil	nil	

Table-5, illustrated that the acute toxicity in term of Anaemia, thrombocytopenia, diarrhoea, neutropenia etc were found more in Arm-I as compared to Arm-II. It was also found significant, P≤ 0.05.

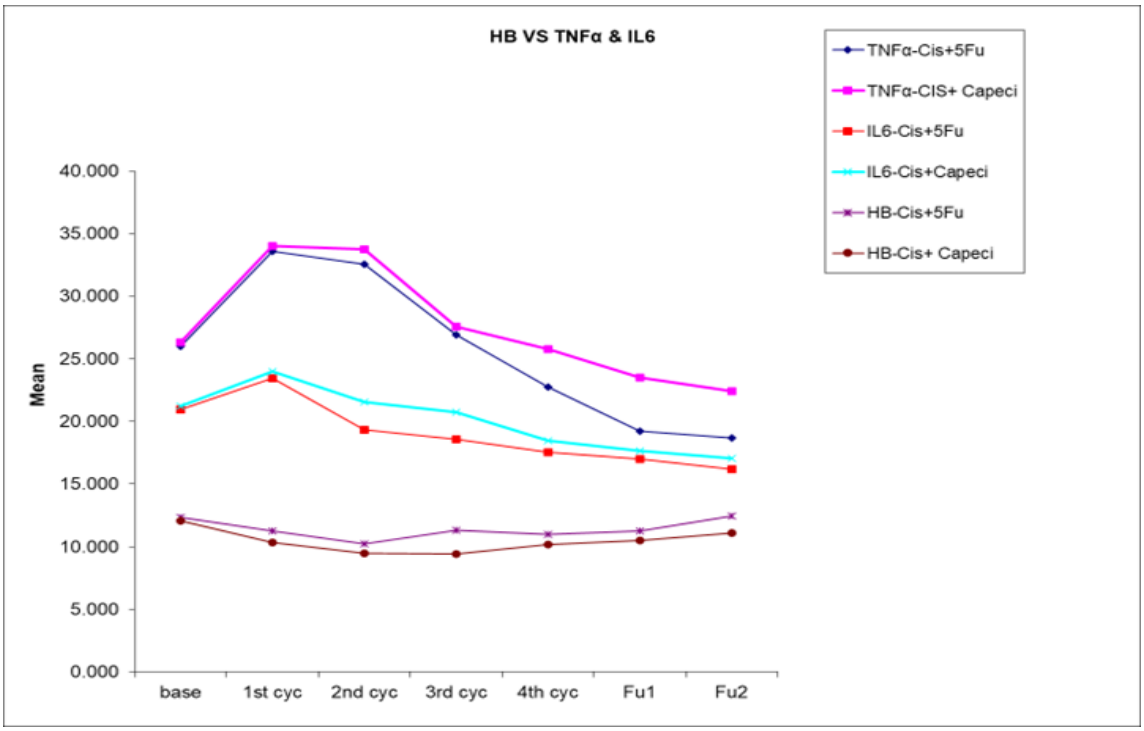

Figure-1: Haemoglobin Level and its Comparison with Tnfα & IL6 in Oral Cancer Patients during Treatment by Cis+ 5Fu; Cis+ Capecitabine

(Tnfα and IL6 were inversely related with Hb; Arm1 was having more treatment response).

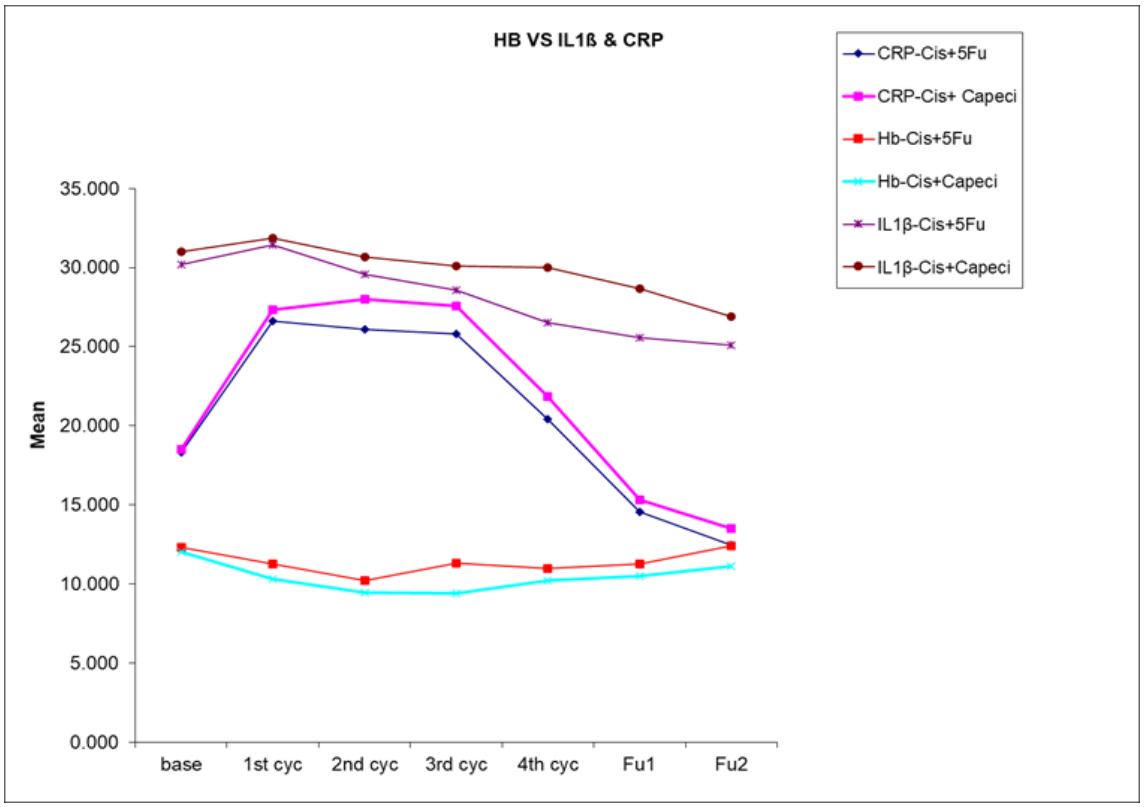

Figure 2: Haemoglobin Level and its Comparison with CRP & IL1β in Oral Cancer Patients during Treatment by Cis+ 5Fu; Cis+ Capecitabine

(CRP and IL1β were inversely related with Hb; Arm1 was having more treatment response).

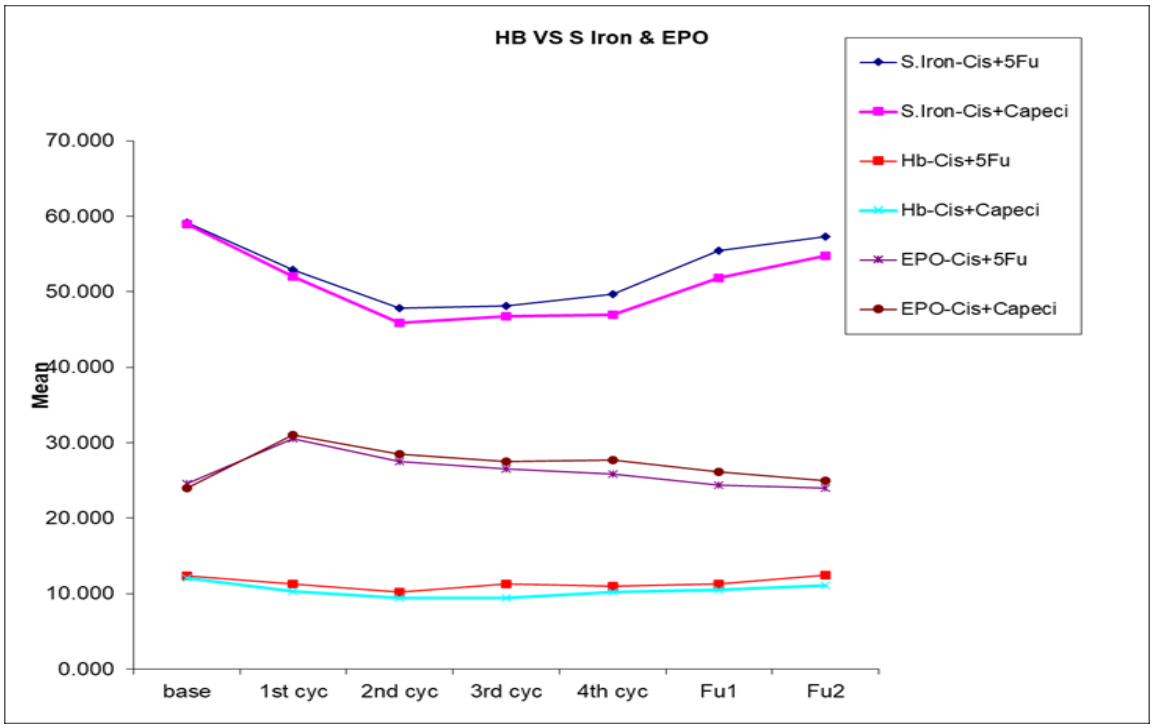

Figure 3: Haemoglobin Level and its Comparison with Serum Iron & EPO in Oral Cancer Patients during Treatment by Cis+ 5Fu; Cis+ Capecitabine

(S. Iron and EPO are directly related with Hb; Arm1 was having more treatment response).

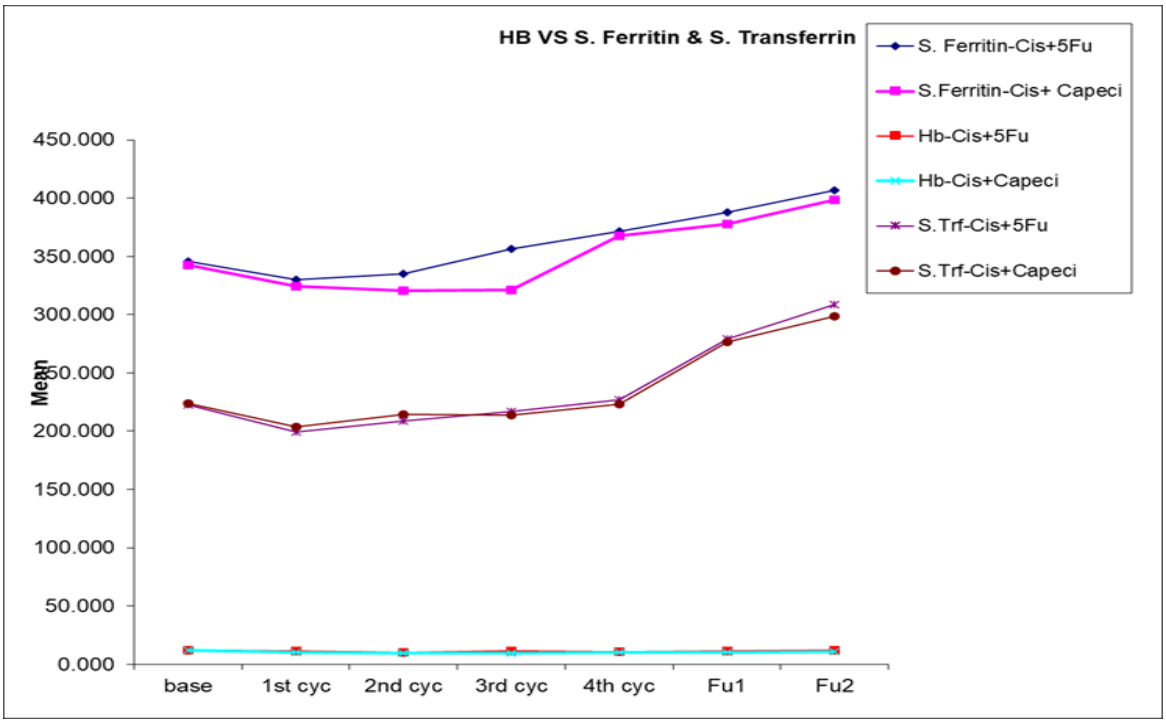

Figure 4: Haemoglobin Level and its Comparison with Serum Ferritin &S. Transferrin in Oral Cancer Patients during Treatment by Cis+ 5Fu; Cis+ Capecitabine

(S. Ferritin and Transferrin are directly related with Hb; Arm1 was having more treatment response).

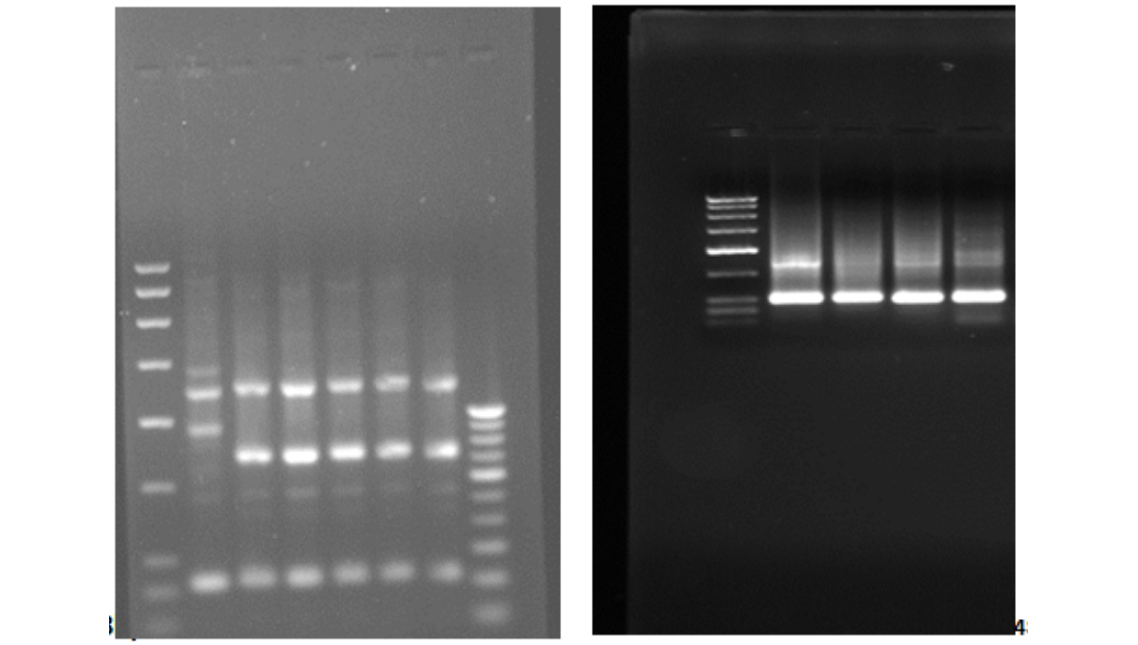

Figure 5: TNFα & IL6 -RT-PCR Positive in Oral Cancer Patients (C=β Actin)

[Detection of mRNAs of TNF-α and IL-6 by RT-PCR. There was amplified expression of mRNA levels of TNF-α (428 bp) and IL-6 (488 bp) in tissues from oral squamous cell carcinoma of the preoperatively non-treated groups]

Discussion

The development of chemotherapy combinations over the last 20 years appears to have plateaued in terms of activity and tolerability. While two-drug regimens remain the standard and are generally tolerated by the majority of patients. Given the modest benefit of chemotherapy, efforts have

focused on bio-chemical-markers that may predict response to chemotherapy. Therefore, the research efforts have shifted from the evaluation of novel chemotherapy drugs and regimens to the incorporation of targeted Bio- chemical parameters/ agents like mRNA, Inflammatory markers etc[37].

In a study it was documented that the concurrent chemoradiotherapy with capecitabine and cisplatin was found to be well tolerated and effective in patients with locally advanced SCCHN the clinical CR rate (78.4%), locoregional control rate (72.6% at 2-year), and progression-free survival rate (57.9% at 2 years) following treatment with the present regimen, which can be administered on an outpatient basis, were comparable with previous results reported for 5-FU and platinum-based concurrent chemoradiotherapy, although the follow-up period was relatively short to compare the survival rate directly. Concurrent chemotherapy with infusion of 5-FU and cisplatin arm achieved a CR rate of 49.4% and 3-year overall survival rate of 27% in a randomised study compared with concurrent chemoradiotherapy with radiation therapy alone [38]. The present study was accordant with the above previous studies. It was also found in a previous study that the TNF-α and IL-6 levels in the homogenates from OSCC tissues detected by ELISA were significantly higher than the levels in normal mucosa [39]. Our results on inflammatory markers were also found similar.

RT-PCR, demonstrated augmented transcript (mRNA) levels of both TNF-α and IL-6 in the tumor tissues and ISH also demonstrated the presence of enhanced transcript signals in tumor cells [39].It was suggested that TNFα enhanced the invasion and metastasis ability of oral cancer cells via the NF-kβ signaling pathway [40]. The present study was agreed with the above previous studies. Serum levels of sTNF RI and sTNF-RII were a more sensitive indicator of progressive cancer and had greater predictive value for detecting cancer than other markers, such as CA 125[41]. It was also reported that the capecitabine was an active and safe substitute for 5-FU in patients with LANPC treated in a neoadjuvant setting [42].

Erythropoietin is a hormone secreted from the kidneys in response to tissue hypoxia and a low serum level-EPO is often seen in anemic cancer patients [26,27].The use of recombinant human erythropoietin (rh-EPO) was introduced as a good alternative to blood transfusions [36]. Our results of EPO, S. Ferritin and Transferrin, which were related to haemoglobin/anemia and subsequently accordant with the above previous studies. Hence, the HB, EPO, TNFα, IL-6 could be used as predictors for diagnostic & treatment-management of oral cancer patients.

Conclusion

A low hemoglobin value in a cancer patient could be itself indicating a poor general condition of the patient, since hypoxia may be an expression of tumor aggressiveness. Similarly elevated Tnfα and IL6 could be indicated a poor general condition of the patients. In conclusion, concurrent chemoradiotherapy with capecitabine and cisplatin was found to be well tolerated and effective in patients with locally advanced head and neck cancer.

Accordingly, this regimen can be regarded as an important chemoradiotherapy option for advanced head and neck cancer, although long-term follow-up is needed to evaluate the late treatment failure and complications.

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