CONCURRENT CHEMORADIOThERAPy WITH DOCETAXEL, CISPLATIN AND 5-FLUOROURACIL (TPF) IN PATIENTS WITH LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK.

Masanori Komatsu, MD, Nobuhiko Oridate, MD, PhD, Takahide Taguchi, MD, PhD, Goushi Nishimura, MD, Phd, Masahiro Takahashi, MD, PhD, Daisuke Sano, MD, PhD, Naoko Sakuma, MD, PhD, Kenichirou Yabuki, MD, Yasuhiro Arai, MD, Junichi Isitoya, MD, PhD, Yasunori Sakuma, MD, PhD, Mariko Hirama, MD, PhD, Osamu Shiono, MD; Department of Otorhinolaryngology and Head and Neck Surgery, Yokohama City University School of Medicine

Background. Compared with radiotherapy alone, concurrent chemoradiotherapy (CCRT) significantly improves survival rates for patients with squamous cell carcinoma of the head and neck (SCCHN). And, several randomized trials demonstrated that a regimen of docetaxel plus cisplatin and 5-fluorouracil (TPF) provides significantly greater benefit to the survival rate of SCCHN patients than does a regimen of cisplatin and 5-fluorouracil in the setting of induction chemotherapy. The aim of this study was to retrospectively evaluate the efficacy, toxicity and long-term prognosis of CCRT with TPF chemotherapy.

Methods. Records of Yokohama City University Hospital (Yokohama, Japan) were retrospectively reviewed to identify patients who had received CCRT with the TPF regimen for histologically proven, previously untreated squamous cell carcinoma of the larynx, oropharynx, or hypopharynx between 2002 and 2012. A total of 142 patients were enrolled and evaluated. Patients were received two cycles of TPF chemotherapy (docetaxel [50mg/m2: day 1], CDDP [60mg/m2: day 4], and continuous 5-fluorouracil [600mg/m2/day: day 1-5]) during definitive radiotherapy.

Results. The overall response rate for primary tumors was 98.5% (130 CR and 10 PR). Among cases with lymph-node involvement, this value for lymph-node was 97.4% (95 CR and 15 PR). The response rates for primary and lymph-node among patients with primary tumors located in the larynx, oropharynx and hypopharynx were 96.9% (29 CR and 2 PR), 98.1% (45 CR and 8 PR), and 96.4% (46 CR and 8 PR), respectively. The 3 and 5-year overall survival rates were 81.2% and 79.1%, respectively, 3 and 5-year disease specific survival (DSS) rates were 82.1% and 80.1%, respectively, and both 3 and 5-year progression free survival (PFS) rates were 68.5%. Among the 32 patients with laryngeal carcinoma, both 3 and 5-year DSS rates were 87.4%. The associated 3 and 5-year PFS rates were both 67.2%. Among the 54 patients with oropharyngeal carcinoma, 3 and 5-year DSS rates were 93.9% and 87.2%, respectively. The associated 3-year and 5-year PFS rates were both 85.2%. Among the 56 patients with hypopharyngeal carcinoma, 3 and 5-year DSS rates were both 70.4%, respectively. The associated 3 and 5-year PFS rates were both 53.7%. Among patients with laryngeal or hypopharyngeal carcinoma, the 5-year laryngectomy-free survival rate was 69.5%. Neutropenia was the most common adverse reaction. Grade 3 and 4 were observed among 50.0% (n=71) and 14.8% (n=21) of patients, respectively. The second and third most frequent severe adverse events were grade 3 dermatitis and mucositis, which occurred in 59.9% and 59.2% of patients, respectively. One hundred three patients (72.5%) completed the scheduled CCRT. There was no death resulting from the treatment.

Conclusions. CCRT with TPF showed excellent survival and organ preservation rates for the patients with locally advanced SCCHN.
**S475 PHASE II TRIAL TO ASSESS TARGETED ORAL ADJUVANT CHEMOPREVENTION IN HIGH-RISK HEAD AND NECK CANCER PATIENTS**

Thomas K Chung, Eben Rosenthal, Lisle Nabell, Lisa Clemons, Renee Desmond, William Carroll; University of Alabama at Birmingham

Background: Preclinical and clinical data has suggested that anti-EGFR therapy may be beneficial as adjuvant therapy in recurrent head and neck squamous cell carcinoma (HNSCC). The purpose of this study was to determine the tolerability and efficacy of long-term treatment of HNSCC after salvage surgery.

Methods: The authors conducted a phase II study of daily erlotinib in patients who completed definitive surgical therapy for recurrent HNSCC. After evaluation by a board-certified otolaryngologist and medical oncologist, patients were enrolled to receive daily doses of erlotinib 150mg for a 12-month period. Patients were followed through their post-operative stay at the discretion of the surgeon but at a minimum were evaluated at 6 months and 12 months. The primary outcome measures were tolerability of prolonged erlotinib therapy and disease-free survival and overall survival at 1 and 2 years.

Results: Thirty-one patients were enrolled into this study. Most patients (19/31) had T3 or T4 recurrent disease at time of salvage surgery. Procedure types included total laryngectomy (11), partial pharyngectomy (10), glossectomy (7), or other (3) and nearly all procedures were of sufficient extent to require free flap reconstruction (27/31). Mean duration of erlotinib therapy was 5 months (range 2-374 days) with 8 patients completing the full course of erlotinib. Of the remaining patients, 7 discontinued therapy due to recurrence, 6 discontinued due to medical or surgical complications deemed unrelated to the study medication and 11 discontinued due to drug-related toxicities. Of the 25 Grade 3 AEs, 4 were classified as possibly related to study medication and included (rash (2), fatigue (1), diarrhea (1)). The most common AEs included acneiform rash (26 patients), fatigue (22), and diarrhea (22). Overall survival was 61% at 1 year and 56% at 2 years. Disease-free survival was 54% at 1 year and 45% at 2 years. Mean time to recurrence (n=16) was 8.7 months. Of the patients who were able to complete 6 months of erlotinib (n=10), overall survival at 2 years was 100% and disease-free survival at 1 year was 90%.

Conclusions: Tolerance of long-term erlotinib was a significant barrier to completion of a 12-month course at conventional dosing levels. However, for those patients that were able to complete 6 months of treatment, recurrence and survival rates were improved in this preliminary cohort. While further study is warranted, erlotinib may be a worthwhile option for patients with aggressive HNSCC.
Purpose/Objective(s):

Head and neck cancer (HNC) patients are at high risk of death from competing risks. This is increasingly relevant in long-term HNC survivors. This report examines the changing mortality profile over time in a randomized trial (RCT) in stage III-IV larynx/pharynx cancer with long term follow-up. The RCT tested the impact of dose intensification delivered prior to full onset accelerated clonogenic proliferation (within 4 weeks) using hyperfractionated (HF) radiotherapy (RT) compared to conventional fractionated (CF) RT in the same overall treatment time. Secondly we wished to consider if "all cause" mortality end-points are optimal in the late assessment of RCTs for these patients.

Materials/Methods:

From 1988-1995, 331 cases were randomized to either HF (58 Gy in 40 fractions twice daily) or CF (51 Gy in 20 fractions once daily). The 5-, 10- and 15-year (yr) actuarial rates of overall survival (OS), locoregional (LRC), distant control (DC), >=Grade 3 late toxicity (LT), and relative risk of deaths were compared between both arms.

Results:

The clinical characteristics were similar between HF (n=169) and CF (n=162). 94% of patients in each arm were smokers. Median follow-up for surviving patients was 13.6 yrs. HF had a 10% 5-yr improved OS (40 vs 30%, p=0.04), but the benefit diminished to 3% at 10-ys (21 vs 18%) and 15-ys (11 vs 8%). A trend towards higher LRC with HF remained (5-yr: 49 vs 40%; 10-yr: 49 vs 39%; 15-yr: 49 vs 39%, p=0.06). DC rates were unchanged (5-yr: 87 vs 85%; 10-yr: 87 vs 84%; 15-yr: 87 vs 84%, p=0.56). LT rates were similar (HF vs CF: 5-yr: 9 vs 12%; 10-yr: 11 vs 14%; 15-yr: 12 vs 16%, p=0.27). Multivariate analysis confirmed that HF reduced the risk of death by 31% [Hazard Ratio (HR) 0.69 (0.55-0.88), p<0.01] and locoregional failure by 30% [HR 0.70 (0.53-0.93), p=0.01] after adjusting for age, performance status, disease site, T- and N-category, and smoking pack-yrs. At last follow-up, 149 deaths had occurred in each arm, of which 105 HF and 115 CF deaths manifested within the initial 5 yrs. Cause of death in this period was mainly from the index cancer (78/105 vs 81/115). After 5-years, the mortality profile evolved (HF vs CF: index cancer: 1 vs 5; other cancer: 23 vs 13; other causes: 18 vs 11, unknown: 6 vs 7). Notably >90% of competing causes of death were smoking--related.

Conclusions:

The RCT, which has the longest follow-up in the MARCH meta-analysis of radiotherapy fractionation, confirms that HF has a 10% effect size 5 yr LRC and OS with comparable LT, but non-index cancer death or smoking morbidity eventually trump the survival effect in longer follow-up. Accurate attribution of cause of death should be applied prospectively and consistently over the time-frame of RCTs to take account of cancer specific death. It may be especially relevant to RCTs requiring long-term follow-up in the current milieu of changing HNC demographics including HPV(+) disease where more than 50%
remain smokers and are still vulnerable to smoking or toxicity-related mortality.
Adenovirus harboring the HSV thymidine kinase (HSVtk) gene under the regulation of a trans-splicing ribozyme targeting human telomerase (hTERT-TR) is cytotoxic to cancer cells by blocking DNA replication. It also induces anti-tumor immunity by activating cytotoxic T cells. Many chemo-reagents also utilize cytotoxic T cells for anti-tumor activity. As human papillomavirus (HPV) positive (+) head and neck squamous cell carcinoma (HNSCC) is increasing globally, the requirement for more effective and less morbid treatment is emerging to improve patient outcome. These cancers are apt to be more immunogenic. Furthermore, head and neck area has been classically a prime target for gene therapy, mainly due to its easier accessibility. Thus, HPV+ HNSCCs could be an attractive target for further vaccine-gene therapy. Here, we explored whether low dose of cisplatin could synergize with TERT-TR-regulated HSVtk to enhance the adenoviral therapeutic efficacy by boosting anti-tumor immunity in HPV (+) HNSCC. Regression of murine tumors was markedly enhanced when low dose (1mg/kg) cisplatin was added to adenovirus-based vaccine expressing HSVtk inside cancer cells, whereas 1mg/kg of cisplatin alone did not suppress the tumor at all in in vivo xenograft models. This effect was abolished by CD8 T cell depletion. Consistent with this, the number of CD8+ T cells inside tumors dramatically increased when adenovirus was combined with cisplatin. Additionally, secondary tumor challenge at a distal site was completely suppressed in mice treated with the combination of adenovirus plus cisplatin. These results suggest that a low dose of cisplatin greatly enhance CD8 T cell-mediated anti-tumor immunity and its addition to HSVtk-based adenovirus permits a big additional benefits to HPV-positive head and neck cancer patients.
DOES ORIGIN WITHIN SUB-MUCOUS FIBROSIS CONFER DIFFERENT BIOLOGICAL STATUS TO ORAL SQUAMOUS CELL CARCINOMA?

Shubhada Kane, MD, Pranjal Kulkarni Kulkarni, MD, Poonam Joshi, MS, Pankaj Chaturvedi, MS; Tata Memorial Hospital, Mumbai, India

Background: Sub-mucous Fibrosis [SMF] is a chronic progressive disorder characterised by fibroelastic change in the lamina propria resulting in restricted mouth opening. This potentially malignant disorder is a major problem related to areca nut chewing in Indian Subcontinent. Oral Squamous cell carcinoma[OSCC] originates in the background of SMF due to disturbances in homeostatic equilibrium between synthesis and degradation of extracellular matrix. Few comparative studies in the literature assess the differences between OSCC with SMF [Group I] and OSCC without SMF [Group II] with special reference to tumour biology of OSCC with SMF.

Objectives: To evaluate the difference in tumour biology in groups of OSCC with and without SMF by comparing Histopathologic variables and expression of biomarkers.

Study Design: Fifty consecutive cases each of Group I and Group II, operated at Tata Memorial Hospital included in this study. Approval for study was taken from hospital IRB. SMF was diagnosed based on established clinical criteria and graded histologically. All HE sections & paraffin blocks were retrieved. Standard Histopathologic variables of primary tumours and metastatic nodes and expression of biomarkers [ survivin, MMP 9, P53 and Mib1] were studied microscopically in both groups. Data entry was performed with SPSS software. The variables were compared in two groups and correlated with node metastasis and extracapsular spread [ECS] in each group. The expression of the biomarkers was compared in both groups and correlated with Histopathologic variables. Chi-square test was used to determine the statistical significance of difference in the Histopathologic variables and expression of biomarkers in two groups and correlation between biomarkers with Histopathologic variables for univariate analysis. Binary logistic regression test was used for the multivariate analysis.

Results with discussion: Comparative study between two groups showed statistically significant difference with Histopathologic variables viz. WHO grade, Brynes’ grade, patterns of invasion [POI], tumour depth, lymphovascular emboli [LVE], pathologic stage, node metastasis, ECS and expression of survivin, mmp9, & MIB1 in univariate analysis. Overall Group I exhibited favourable Histopathologic variables in higher percentage of cases as compared to Group II. Significant difference was not observed with host response , distance of closest cut margin and perineural invasion. However the expression of survivin was the only significant variable in comparative study by Multivariate analysis.

When all the variables, were correlated with node metastasis and ECS in each group individually, significant correlation was observed in WHO grade, POI and mmp 9 expression with node metastasis in Group I by univariate analysis but not by Multivariate analysis. Statistically significant correlation was noted when survivin, MMP9 and MIB1 expression and LVE were correlated with presence of node metastasis and ECS in Group II respectively. However LVE was the only significant variable for ECS in Group II by Multivariate analysis.

Conclusion:

OSCC arising in the background of SMF is biologically less aggressive than OSCC without SMF & hence is a favourable clinico-pathologic entity.
LVE is significantly correlated with ECS in OSCC without SMF

Survivin expression can be used as an independent prognostic marker in OSCC.