ADVANCES IN ORAL MEDICINE from Bench to Bedside to Bench
AAOM 2018

Lester Burket Memorial Award
Thursday, 04/12/2018, 11:00-11:45am

*Presenter/Awardee

To conserve space, we list only the institution and the country submitted as 1st organization.

Abstracts Committee:
Chair: Kentaro Ikeda, DDS, MPH
Co-Chair: Bhavik Desai, DMD, PhD

11:00am

Timing of Pre-Radiation Dental Treatment and Risk of Osteoradionecrosis

*J. Amadeo Valdez, Abriana Gresham, Nigel Rozario, Joel J. Napenas, Michael T. Brennan,
Carolinas Healthcare System, USA

Objectives:

Per the consensus proposed by The National Institute of Health in 1989, head and neck cancer (HNC) patients must undergo a thorough dental evaluation to identify potential oral conditions that can affect the course of RT. If needed, invasive dental procedures are recommended before RT because of the increased risk of ORN due to the disturbances in wound healing caused by RT. Guidelines of pre-RT dental treatment vary due to the lack of sufficient scientific evidence to establish a protocol; there is limited knowledge about the influence of the timing of pre-RT prophylactic dental treatment on ORN among HNC patients.

The aim of this study is to determine the risk of developing ORN in relation to the timing of invasive pre-RT dental treatments and provide more evidence-based guidelines for pre-RT dental management. We hypothesized that the less time between dental treatment and RT the higher risk of developing ORN among patients with HNC.

Methods:

This was a retrospective cohort study of HNC patients who received RT and were treated with prophylactic dental procedures within Carolinas HealthCare System between July 2010 and July 2017. Records of patients with HNC were located per the selected diagnostic codes that appropriately identify squamous cell carcinoma of the head and neck, treatment with RT, and ORN diagnoses if applicable. The following variables were collected: demographics, social and medical history, cancer diagnosis, baseline dental conditions, dental procedures, cancer treatments, and ORN diagnosis. To be included on the study patients had to be 18 years or older, have a diagnoses of squamous cell carcinoma of the head or neck, received at least 5000 cGy of RT to the maxilla or mandible and have pre-RT dental treatment. The diagnosis of ORN was confirmed with pathology reports and clinical notes. Patients with a prior ORN diagnosis, history of RT to the head and neck or insufficient data were excluded.

Descriptive statistics in the form of mean and standard deviations for continuous variables and frequencies and percentages for categorical variables were calculated. A univariate analysis (t-test and chi-square test or non-parametric test, when appropriate) was completed to compare ORN cases vs non-cases.

Results:

We identified 355 HNC cases with pre-RT dental treatment that met the inclusion criteria. Of this cohort 276 (77.7%) were males, 252 (71%) were white, 227 (66.6%) had a history of tobacco use and 222 (65.3%) had a history of alcohol consumption. The two most common HNC sites were tonsil with 77 cases (21.7%) and base of tongue with 55 cases (15.5%).

Regarding cancer treatment, 243 (70%) patients received concomitant chemotherapy, the mean RT dose was 6,684.91 cGy (± 491.6) and the mean number of fractions was 33.28 (± 3.59).

At initial dental visit, 166 (54%) patients presented with moderate to severe periodontitis. The mean DMFT score was 14.79 (± 9.71) and the mean number of present teeth was 7.63 (± 8.55). Of those that received pre-RT dental treatment, 215 patients (68.9%) had dental extractions, 130 (67.5%), had dental cleaning and 27 (15.5%) underwent tori removal. In this cohort, 14 (3.9%) patients developed ORN after RT on the extraction site.

In patients with ORN, the mean number of teeth extracted pre-RT was 2.50 (± 7.37) vs non-ORN 0.20 (± 1.96) ($p = 0.0019$). Within the patients with ORN, 12 (80%) patients had moderate to severe periodontitis as compared to patients without ORN, 131 (52. 61%) ($p = 0.0387$).

There was no significant difference between the means of the two groups in the following variables: days between pre-RT extractions and RT: 29.34 ± 23.86 vs non-ORN 23.17 ± 13.93 ($p = 0.1145$), days between pre-RT tori removal and RT 29.73 ± 21.81 vs non-ORN 28 ± 0 ($p = 0.6852$), days between pre-RT dental cleaning and RT 27.63 ± 25.68 vs non-ORN 34.25 ± 12.58 ($p = 0.4028$).

Conclusions:

There was a significant difference in the number of extractions and periodontal status within the ORN cases vs the non-cases. There was no significant difference in the time between dental treatment and start of RT for ORN cases vs non- cases. This data supports the notion that patients with a higher number of extractions prior RT and poor periodontal health are at higher risk of developing ORN

11:20am

Combined PI3K/mTOR Inhibition and Transcriptional Repression in Head and Neck Carcinoma

Tiffany Tavares, Maria Rusan, Peter S. Hammerman, Ann Marie Egloff, Ravindra Uppaluri,
Harvard School of Dental Medicine, USA

Objectives:

Head and neck squamous cell carcinoma (HNSCC) is the fifth most common cancer worldwide. Modest responses to targeted therapy for HNSCC have been observed and are limited by tumor heterogeneity and adaptive resistance. Combination therapy has been proposed to mitigate the difficulties in sustaining responses with targeted therapy. Genomic characterization and preclinical studies have shown frequent phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway in HNSCC. Several PI3K and mTOR inhibitors have been tested in clinical trials with modest responses to date. Recent preclinical studies have shown promising results in diverse cellular models with novel, covalent cyclin-dependent kinase (CDK) inhibitors such as THZ1 when administered in combination with targeted kinase inhibitors. Our objective was to investigate the potential combinatorial effect of PI3K/mTOR pathway inhibition with THZ1 transcriptional repression in PI3K/mTOR dependent models of HNSCC as a means to enhance therapeutic response and to elucidate the key components of the pathway responsible for the effect.

Methods:

Five HPV-negative HNSCC cell lines with diverse alterations in the PI3K/mTOR pathway were selected (CAL33, HSC-4, YD8, SCC-25, and SNU-899). YD8 [MR2] which does not have reported PI3K/mTOR alterations was used as a negative control. EC50 doses were defined with cell proliferation assays for the following inhibitors: NVP-BEZ235 (dual PI3K/mTOR), BKM-120 (PI3K), rapamycin (mTORC1), torin2 (dual mTORC1/mTORC2), and THZ1 (CDK7/12) at 96 hours. Colony formation assays in a 24-well format with monotherapy and combination therapy at 4 weeks and immunoblotting for components of the PI3K/mTOR pathway and RNA polymerase II, a downstream target of THZ1, were also performed. Uniform doses of both NVP-BEZ235 and THZ1 were applied to colony formation and immunoblotting across all cell lines.

Results:

Among the PI3K/mTOR inhibitors tested, NVP-BEZ235 and torin2 demonstrated EC50s below or near 100 nM in all cell lines and were effective in combination with THZ1 in colony formation assays. We focused on NVP-BEZ235 as this inhibitor is more advanced with regards to clinical development. Monotherapy with NVP-BEZ235 or THZ1 was ineffective, but increasing doses of both THZ1 and NVP-BEZ235 in combination demonstrated reduction in cell proliferation particularly at doses near or above EC50 in 4/5 lines. SCC-25 showed an enhanced effect achieving significant cell death at doses below EC50 for both drugs in combination. Addition of THZ1 to NVP-BEZ235 in cell proliferation assays demonstrated significant EC50 shift. Immunoblotting for downstream effectors of the PI3K/mTOR pathway corroborated the phenotype observed in a dose-dependent fashion.

Conclusion:

PI3K/mTOR pathway is frequently altered in HNSCC and, in this context, dual PI3K/mTOR inhibition in combination with THZ1 may be a therapeutic strategy with sustained response.