

INNOVATIVE APPROACH FOR RISK STRATIFICATION OF PATIENTS ON



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Objectives: Osteonecrosis of the jaw (ONJ) may affect up to 18% of cancer patients treated with bisphosphonates. In many cases, dento-alveolar surgery is associated with the development of bisphosphonate-related ONJ (BRONJ). To date, there is no reliable assay to predict the risk of developing BRONJ. This reported trial is a multi-center, international study, aiming to unravel SNPs associated with BRONJ and to stratify the risk for ONJ.

Methods: We sequenced 125 exomes of subjects receiving bisphosphonates due to multiple myeloma (106 patients) or other cancers (19 patients). Of these, 69 patients had BRONJ and 56 were disease-free for at least two years. Bioinformatics was performed as follows: short reads were mapped to a reference human genome with BWA aligner and variant calling was performed using the FreeBayes pipeline. Samples were divided into Training/Testing sets. We used PLINK to find candidate SNPs in the Training set and then to test them in the Testing set.

Results: We found six SNPs that were associated with BRONJ (Thresholds were: $P < .05$ with False Positive Rate $< 20\%$ in both sets). Additionally, 13 SNPs located in three genes showed association with the disease in an ethnicity-dependent manner. Some of these SNPs reside in genes with biological functions possibly relevant to the etiology of BRONJ. A statistical model yielded 93% sensitivity among cancer patients who developed BRONJ, and 68% specificity among BRONJ-free cancer patients.

Conclusions: The 19 SNPs associated with BRONJ were discovered on a single sample set and tested on an independent set, which strengthens their reliability. Since there is no effective treatment for BRONJ, combining these SNPs into a predicting algorithm is instrumental in stratifying BRONJ risk in patients administrated with bisphosphonates who are candidate for dental surgery. Moreover, a predictive algorithm may be utilized by oncologists for the management of high-risk patients, and by dentists for personalized treatment plan.