Metastatic Penile, Uterine Cervical and Skin Squamous Cell Carcinomas: A Comparative Genomic Profiling Study

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ABSTRACT

Background: We compared the genomic alteration (GA) profiles of metastatic squamous cell carcinoma (mSCC) of the penis (mPSCC), cervix (mSCC), and skin (mSSCC) to study impact on the targeted and immunotherapy options for the men and women suffering from these refractory cancers.

Methods: 78 mPSCC, 604 mSCC and 338 mSSCC underwent CGP using a hybrid-capture based assay. Tumor mutational burden (TMB) was determined on 0.83-1.14 megabase pairs (Mb) of sequenced DNA and reported as mutations/Mb (mut/Mb), and microsatellite instability (MSI) was determined on 114 loci.

Results: The HPV+/CDKN2A- status was significantly more frequent in the mSCC than mPSCC or mSCC (P=0.0001). The GA/tumor frequencies were similar for mSCC and mPSCC, but significantly higher in mSSCC compared to mPSCC. TP53 mutations were more common in mSSCC (UV light exposure) and mPSCC (likely due to loss of an original HPV+ status). TERT, NOTCH1 and FAT1 GA were more frequent in mPSCC and mSSCC whereas PIK3CA GA were more common in mSCC. mTOR pathway targets (GA in STK11, FBXW7 and PTEN) were more common in mSSCC than mPSCC or mSCC. MSI high status was extremely rare in all cases. TMB ≥10/20 mut/Mb frequencies were noteworthy in mPSCC and mSSCC but extraordinarily high in mSCC.

Conclusions: Although mSSCC, mPSCC and mSCC share a variety of clinicopathologic features, the 3 tumor types can be sharply differentiated on CGP. The TP53, CDKN2A and HPV status of these tumor types differ significantly with HPV+ higher in the mSCC group. There are opportunities for targeted therapies in all groups predominately identified in the mTOR pathway. The relatively high numbers of cases with significantly elevated TMB in all 3 tumor types suggest that immunotherapies would be beneficial in a large subset of patients.

MATERIALS AND METHODS

- ≥50 ng DNA extracted from 40 µm of FFPE sections
- Sequencing performed for up to 315 cancer-related genes and introns from 28 genes commonly rearranged in cancer
- Hybrid capture-based sequencing using adaptor ligation-based libraries
- Mean coverage depth ≥600X
- Base substitutions, insertions and deletions (short variants; SV), rearrangements, and copy number changes were assessed
- Tumor mutational burden (TMB) calculated from 0.83-1.14 Mb sequenced DNA, reported as mutations/Mb (mut/Mb), and microsatellite instability (MSI) was determined on 114 loci.

RESULTS

- The HPV+/CDKN2A- status significantly more frequent in the mSCC than mPSCC or mSSCC (P=0.0001)
- The GA/tumor frequencies were similar for mSCC and mPSCC, but significantly higher in mSSCC (P<0.0001)
- TP53 mutations were more common in mSSCC (UV light exposure) and mPSCC
- TERT, NOTCH1 and FAT1 GA were more frequent in mPSCC and mSSCC whereas PIK3CA GA were more common in mSCC
- mTOR pathway targets (GA in STK11, FBXW7 and PTEN) were more common in mSSCC than mPSCC or mSCC
- MSI high status was extremely rare in all cases
- TMB ≥10/20 mut/Mb frequencies were noteworthy in mPSCC and mSSCC but extraordinarily high in mSCC

CASES

Online interactive display of all cases

CONCLUSIONS

- mSCC, mPSCC and mSSCC share clinicopathologic features
- However, the 3 tumor types can be sharply differentiated on CGP
- The TP53, CDKN2A and HPV status of the tumor types differ significantly with HPV+ higher in the mSCC group
- There are opportunities for targeted therapies in all groups predominately identified in the mTOR pathway
- The relatively high numbers of cases with significantly elevated TMB in all 3 tumor types suggest that immunotherapies would be beneficial in a large subset of these patients