Abstract

BACKGROUND: Surgery and radiation are the standard treatment options for meningiomas; however, this is not always feasible. Expression profiling was performed to determine the presence of actionable biomarkers and to provide rationale for treatment directed at them.

METHODS: Meningioma patients were profiled by Caris Life Sciences using immunohistochemistry (IHC) to detect PD-1 on tumor-infiltrating lymphocytes and PD-L1 on tumor cells with the SP142 antibody. Next-generation sequencing, pyrosequencing, IHC, fragment analysis, and fluorescence in situ hybridization were used to determine mutational and expression status.

RESULTS: A total of 115 meningioma tumors were analyzed across grades I (n=22), II (n=36), III (n=23), and grade unclear (n=28). The median age of the cohort was 60, with a range spanning 6-90 years; 52% were female. The most frequent mutation (frameshift or truncating) across all grades was IDH1/2 mutations, which were identified in 33% (36/115) of meningiomas. TOP2A and thymidylate synthase (TS) mutations were the most frequent across all grades; however, their contribution was significantly higher in grade III tumors (p<0.05).

Background

Meningioma is the most common primary tumor of the central nervous system in adulthood. While WHO grade 1 tumors are histopathologically benign, a significant portion may experience recurrence. Furthermore, atypical (grade II) or anaplastic (grade III) meningioma present a more aggressive clinical course with the recurrent tumors often becoming refractory to surgery or radiation.

Genetic alterations including NF2, AKT3 and SMO have been shown to be important in the molecular pathogenesis of meningioma and may serve as therapeutic targets. We aim to use a combination of multiple technologies to interrogate the molecular alterations including protein expression and gene mutations in a large cohort of meningioma that could potentially direct therapy and provide insights to treatment options including chemo-therapeutic, targeted or immune-modulatory agents.

Results

Figure 1: Patient characteristics

Figure 2: A) Protein expression frequencies in the 115 meningioma tumors studied; B) Selected protein expression frequencies in grade 1, 2 and 3 meningiomas. A line indicates statistically significant difference found between different grades of tumors (p<0.05).

Figure 3: Mutations frequencies seen in the meningioma cohorts studied; A) Mutations found in the meningioma cohorts studied; B) Gene amplification frequencies in meningioma tumors.

Results, continued

Table 1: Specific protein changes found in each subgroup of meningiomas

Conclusions

1. There was a high prevalence of NF2 gene amplification in meningioma, especially in grade II and III subgroups supporting the investigation of FAK inhibitors in these tumors.

2. Aberrant activation of PIK3CA/Akt/mTor pathway as shown by PTCH1 mutation in grade II and III subgroups supporting the investigation of FAK inhibitors in these tumors.

3. Significantly elevated TOP2A and TS expression in grade III tumors is in line with the highly aggressive nature of the disease and suggest the potential utility of TOP2A inhibitors but also the lack of utility of fluoropyrimidines including 5-FU and capecitabine  in malignant meningioma.

4. Activation of PD-1/PD-L1 axis suggests the opportunities for targeted therapies in select subsets of patients.

References

• Yasseen, S., et al. (2016) “Clinical impact of targeted amplion sequencing for meningiomas as a practical clinical sequencing system” Modern Pathology (2016), 1-6


• The average age and female prevalence increase as tumor grade increases; however the differences are not significant.