




Effects on survival of *BAP1* and *PBRM1* mutations in sporadic clear-cell renal-cell carcinoma: a retrospective analysis with independent validation

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Summary

Background

Clear-cell renal-cell carcinomas display divergent clinical behaviours. However, the molecular genetic events driving these behaviours are unknown. We discovered that *BAP1* is mutated in about 15% of clear-cell renal-cell carcinoma, and that *BAP1* and *PBRM1* mutations are largely mutually exclusive. The aim of this study was to investigate the clinicopathological significance of these molecular subtypes and to determine whether patients with *BAP1*-mutant and *PBRM1*-mutant tumours had different overall survival.

Methods

In this retrospective analysis, we assessed 145 patients with primary clear-cell renal-cell carcinoma and defined *PBRM1* and *BAP1* mutation status from the University of Texas Southwestern Medical Center (UTSW), TX, USA, between 1998 and 2011. We classified patients into those with *BAP1*-mutant tumours and those with tumours exclusively mutated for *PBRM1* (*PBRM1*-mutant). We used a second independent cohort (n=327) from The Cancer Genome Atlas (TCGA) for validation. In both cohorts, more than 80% of patients had localised or locoregional disease at presentation. Overall both cohorts were similar, although the TCGA had more patients with metastatic and higher-grade disease, and more TCGA patients presented before molecularly targeted therapies became available.

Findings

The median overall survival in the UTSW cohort was significantly shorter for patients with *BAP1*-mutant tumours (4.6 years; 95% CI 2.1–7.2), than for patients with *PBRM1*-mutant tumours (10.6 years; 9.8–11.5), corresponding to a HR of 2.7 (95% CI 0.99–7.6, p=0.044). Median overall survival in the TCGA cohort was 1.9 years (95% CI 0.6–3.3) for patients with *BAP1*-mutant tumours and 5.4 years (4.0–6.8) for those with *PBRM1*-mutant tumours. A HR similar to the UTSW cohort was noted in the TCGA cohort (2.8; 95% CI 1.4–5.9; p=0.004). Patients with mutations in both *BAP1* and *PBRM1*, although a minority (three in UTSW cohort and four in TCGA cohort), had the worst overall survival (median 2.1 years, 95% CI 0.3–3.8, for the UTSW cohort, and 0.2 years, 0.0–1.2, for the TCGA cohort).

Interpretation

Our findings identify mutation-defined subtypes of clear-cell renal-cell carcinoma with distinct clinical outcomes, a high-risk *BAP1*-mutant group and a favourable *PBRM1*-mutant group. These data establish the basis for a molecular genetic classification of clear-cell renal-cell carcinoma that could influence treatment decisions in the future. The existence of different molecular subtypes with disparate outcomes should be considered in the design and assessment of clinical studies.

Funding

Cancer Prevention and Research Institution of Texas and National Cancer Institute.

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
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