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< Previous Article | Next Article >

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.

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