Prostate cancer metastatic profiles correlate with molecular alterations

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Introduction

• Mutational and molecular signatures that were characterized in advanced prostate cancers (PCa) suggested new insights in targetable pathways for disease management (1).
• Notably, patients with metastatic PCa have been shown to harbor germline, as well as somatic, mutations of DNA repair genes (2,3).
• To establish correlations between clinical profile, germline and somatic alterations, targeted next generation sequencing (NGS) was performed on a cohort of 153 PCa patients.

Results

• The 5 MSI positive tumors (4.0%) showed the highest TMB values (median TMB 19.03/Mb for MSI+ vs 1.27/Mb for MSI-, P=0.0002; Figure 1) and were characterized by extensive loco-regional involvement without bone metastasis (Table 2).

Figure 1: Median Tumor Mutational Burden (TMB) by MSI status

• Mutations in TP53 were the most frequent somatic alterations (28.6%) (Figure 2), and were associated with a higher risk of metastases in other sites than bone (P=0.0001; Table 2).

Figure 2: Most frequent somatic mutations

• The 4 patients (3.2%) who harbored a biallelic mutation of CDK12 all had bone metastasis (Table 2).
• An HRD score > 29 was observed in 19.6% of the tumors, was more frequent among patients with a germline mutation (36.4% vs 15.0%, P=0.035; Figure 3), and was associated with a higher risk of bone metastasis (P=0.034; Table 2).

Figure 3: MyChoice Homologous Recombination Deficiency (HRD) score in patients with or without germline mutation

• Patients with a germline or somatic mutation of BRCA2 had a higher median HRD score (P=0.026; Figure 4), and were characterized by a higher risk of death by PCa (P=0.0085, Table 2).

Figure 4: Median MyChoice HRD score in patients with or without BRCA2 mutation

Methods

• Retrospective cohort of 153 patients with advanced PCa (Table 1).
• DNA was extracted from retrospective paraffin embedded tumoral tissues and blood (or saliva) from each patient.
• Next generation sequencing targeting coding regions of 111 candidate genes
• DNA repair deficiency in tumors was assessed by establishing microsatellite instability status (MSI), tumor mutational burden (TMB) and myChoice (Myriad Genetics) homologous recombination deficiency (HRD) score.

Table 1: Characteristics of the patients

| Median age at diagnosis (range) | 68.5 (45-92) |
| Median age at metastatic diagnosis (range) | 70 (45-92) |
| Stage | M1 117 (76.5%) 108 (70.6%) |
| Ancestry | European (White Caucasian) 75 (49.0%) 67 (43.8%) 11 (7.2%) |

Table 2: Correlation between somatic alterations and clinical profile

| Somatic/ Germline alteration | Percentage of patients | Patient Characteristics |
| MSI Positive Tumor | 4% | Extensive locoregional extension without bone metastasis |
| TP53 somatic mutation | 28.6% | Higher risk of metastases in other sites than bone |
| Biallelic CDK12 mutation | 3.2% | Bone metastasis |
| HRD Score > 29 | 19.7% | Higher risk of bone metastasis |
| BRCA2 mutation | 5.9% | Higher risk of death by PCa |

Conclusion

Among these patients with advanced PCa, we identified molecular alterations associated with different clinical profiles: MSI+ tumors associated with loco-regional involvement without bone metastasis, mutations of TP53 associated with a higher risk of metastases in other sites than bone, biallelic mutation of CDK12 and HRD score >29 associated with the presence of bone metastasis, and lastly, BRCA2 mutation associated with a higher risk of death by prostate cancer.

Conflicts of interest & Support

Olivier Cussenot has has nothing to declare.
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