Frequency and clinical significance of homologous recombination deficiency gene mutations in non-cutaneous melanoma

北京大学肿瘤医院
BEIJING CANCER HOSPITAL

Yue Yang, Bin Lian, Lu Si, ZhiHong Chi, XiNan Sheng, Yan Kong, ChuanLiang Cui, Jun Guo*
Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China.

Background

- Homologous recombination deficiency (HRD) refers to the state of tumor cells which received defects in DNA-damage repair mechanisms. The HRD phenotype encodes important proteins for DNA homologous recombination repair (HRR) which can serve as a biomarker of therapeutic efficacy. Here, we explored the frequency and clinical significance of HRD gene mutations in non-cutaneous melanoma to provide experience for clinical options.

Methods

- The data of 932 Chinese non-cutaneous melanoma patients using next-generation sequencing techniques with 81 or 425 cancer-related genes were collected. Among them, 852 patients were detected with 81 genes and 80 with 425 genes. The survival analysis was used to find the correlations between HRR gene mutations and clinical outcomes.

Results

- In non-cutaneous patients, 9.9% (92/932) patients were found the genomic alterations in HRR genes. The frequently mutated genes were ATM (3.5%), ARID1A (3.4%), BRCA2 (2.7%), BRCA1 (1.8%), ATR (0.2%), ARID2 (0.2%), BRIP1 (0.1%), PALB2 (0.1%), FANCA (0.1%) and RAD50 (0.1%). Among 92 patients with HRR gene mutation, 53.3% were males and 67.4% were under 65 years old. 27 patients were acral melanoma, 41 patients with mucosal melanoma, 6 patients with uveal melanoma and 18 patients with unknown melanoma. In addition, 32.6% had ulcer in primary sites. 25.0% were in stage IV and 3 patients were with M1a, 2 with M1b, 14 with M1c, 4 with M1d. 56.5% patients received the first-line treatment, 20.7% received the second-line treatment and 8.7% received the third-line treatment. And 22 patients underwent anti-PD-1 therapy. From January 2008 to January 2022, the median follow-up time of all the patients was 26.6 months (95% CI: 24.6-28.6 months). 36 patients among 92 patients with HRR gene mutation died and the median overall survival (OS) was not reached. The 1-year, 3-year and 5-year survival rates were 85.2%, 55.1%, 48.8%, respectively. Meanwhile, 310 in 840 patients without HRR gene mutation died eventually. The median OS was also not reached and the 1-year, 3-year and 5-year survival rates were 80.1%, 53.0%, 44.4%, respectively.

Conclusions

ATM and ARID1A are the most common genomic alterations with HRR genes and patients with HRR gene mutations maybe get survival benefits from treatment.

Table 1. Patient characteristics

Characteristics	Total (n=932)
Age (years)	
<65	655 (70.3)
≥65	277 (29.7)
Sex	
Male	436 (46.8)
Female	496 (53.2)
Primary site	
Acral	336 (36.1)
Mucosal	418 (44.8)
Uveal	34 (3.6)
Unknown	144 (15.5)
Ulcer	
No	157 (16.8)
Yes	363 (38.9)
Unknown	412 (44.2)
Stage	
I	150 (16.1)
II	275 (29.5)
III	258 (27.7)
IV	184 (19.7)
NA	65 (7.0)
M stage	
0	713 (76.5)
1a	32 (3.4)
1b	32 (3.4)
1c	98 (10.5)
1d	21 (2.3)
NA	36 (3.9)

Note: Data are shown as n (%).

Table 3. HRD gene distribution

HRD genes	Total (n=92)
ATM	33 (35.9)
ARID1A	32 (34.8)
BRCA2	25 (27.2)
BRCA1	17 (18.5)
ATR	2 (2.2)
ARID2	2 (2.2)
BRIP1	1 (1.1)
PALB2	1 (1.1)
FANCA	1 (1.1)
RAD50	1 (1.1)

Note: Data are shown as n (%).
Abbreviations: HRD, Homologous recombination deficiency
Correlation of clinical characteristics between patients with and without HRD gene mutations

Table 2. Patient with HRD gene mutation characteristics

Characteristics	Total (n=92)
Age (years)	
<65	62 (67.4)
≥65	30 (32.6)
Sex	
Male	49 (53.3)
Female	43 (46.7)
Primary site	
Acral	27 (29.3)
Mucosal	41 (44.6)
Uveal	6 (6.5)
Unknown	18 (19.6)
Ulcer	
No	14 (15.2)
Yes	30 (32.6)
Unknown	48 (52.2)
Stage	
I	31 (33.7)
II	15 (16.3)
III	22 (23.9)
IV	23 (25.0)
NA	1 (1.1)
M stage	
0	68 (73.9)
1a	3 (3.43
1b	2 (2.2)
1c	14 (15.2)
1d	4 (4.3)
NA	1(1.1)
The line of prior therapy	
1	52 (56.5)
2	19 (20.7)
3	8 (8.7)
≥4	5 (5.4)
Prior immunotherapy	
Yes	39 (42.4)
No	53 (57.6)
Prior chemotherapy	
Yes	31 (33.7)
No	61 (66.3)

Note: Data are shown as n (%).
Abbreviations: HRD, Homologous recombination deficiency

Table5. The 1-year, 3-year, 5-year survival rates

Characteristics	1-year (%)	3-year (%)	5-year (%)
Total (n=932)	80.1	53.3	44.7
HR non-deficient (n=840)	80.1	53.0	44.4
HR deficient (n=92)	85.2	55.1	48.8

Table 4. Correlation of clinical characteristics between patients with and without HRD gene mutations

Characteristics	HR non-deficient (n=840)	HR deficient (n=92)	P
Age (years)			0.523
<65	593 (70.6)	62 (67.4)	
≥65	247 (29.4)	30 (32.6)	
Sex			0.394
Male	386 (46.0)	49 (53.3)	
Female	453 (53.9)	43 (46.7)	
Primary site			0.195
Acral	309 (36.8)	27 (29.3)	
Mucosal	377 (44.9)	41 (44.6)	
Uveal	28 (3.3)	6 (6.5)	
Unknown	126 (15.0)	18 (19.6)	
Ulcer			0.262
No	143 (17.0)	14 (15.2)	
Yes	333 (39.6)	30 (32.6)	
Unknown	364 (43.3)	48 (52.2)	
Stage			<0.001
I	118 (14.0)	31 (33.7)	
II	261 (31.1)	15 (16.3)	
III	236 (28.1)	22 (23.9)	
IV	161 (19.2)	23 (25.0)	
NA	64 (7.6)	1 (1.1)	
M stage			0.190
0	645 (76.8)	68 (73.9)	
1a	29 (3.5)	3 (3.43	
1b	31 (3.7)	2 (2.2)	
1c	83 (9.9)	14 (15.2)	
1d	17 (2.0)	4 (4.3)	
NA	35 (4.2)	1(1.1)	

Note: Data are shown as n (%).
Abbreviations: HR, Homologous recombination; HRD, Homologous recombination deficiency

Survival analysis and prognosis of patients with and without HRD gene mutations
The median follow-up time of all the patients was 26.6 months (95% CI: 24.6-28.6 months).
Among them, 346 patients died and the median overall survival (OS) was not reached.
Chemotherapy was likely to provide a survival benefit to patients with HRD gene mutations because the 3-year survival rates were 75.0% versus 51.6%.
Immunotherapy was not correlated with better prognosis as the 3-year survival rates were 52.0% versus 57.1%.