MDM2/4 amplification predicts poor response to immune checkpoint inhibitors: a pan-cancer analysis

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INTRODUCTION

The revolutionary immune checkpoint inhibitors (ICI) treatment has been a landmark of cancer therapy, with long-term survival benefit in advanced cancer patients reported.[1] In another aspect, relatively low response rates and hyperprogression remain to be solved in immunotherapy.[2 3] There have been some known biomarkers for the prediction of ICI efficacy, such as programmed death-ligand 1 expression, tumour mutational burden (TMB), microsatellite instability (MSI) and mismatch-repair deficiency. The ongoing effort to identify predictive biomarkers is still of great significance. MDM2/4 amplification (AMP) has been reported to be related with hyperprogression during ICI therapy in several cancer types.[4–6] But previous studies concerning MDM2/4 AMP were of limited sample size and still require more clinical data support. In this study, we aimed to estimate the prevalence of MDM2 AMP across multiple cancer types and explore its role in the prediction of benefit from ICI treatment.

METHODS

We estimated the prevalence of MDM2/4 AMP in 250 studies involving 30118 patients from the cBioPortal database (https://www.cbioportal.org). An ICI treatment cohort of 1105 patients obtained from MSK-IMPACT Clinical Sequencing Cohort (MSKCC) was utilised to explore the relationship between MDM2/4 AMP and ICI treatment. The overall survival (OS, calculated from the ICI start date) was calculated using the Kaplan-Meier method and compared between groups (p values by log-rank test). We also performed a multivariable Cox regression analysis, to explore whether MDM2/4 AMP can be an independent predictive biomarker from the known ones, including MSI and TMB. These patients were sequenced by MSK-IMPACT targeted next-generation sequencing (NGS) assay (341-gene (226 patients, 20.5%), 410-gene (869 patients, 78.6%) and 468-gene (10 patients, 10%)). The median of TMB (cut-off: 12 mut/Mb) was used to divided patients into TMB-high and TMB-low groups. Finally, we compared the OS (calculated from the date of first chemotherapy infusion) of 2285 non-ICI treated patients from MSKCC according to their MDM2/4 AMP status to determine whether MDM2/4 AMP is a prognostic or predictive biomarker of response.

RESULTS

The prevalence of MDM2/4 AMP in the 30118 patients with different cancer types ranged from 0.2% to 21.2% (figure 1D). Several kinds of cancer were observed to have relatively higher prevalence, including soft tissue sarcoma (21.2%), breast cancer (14.2%), stomach adenocarcinoma (8.5%), prostate adenocarcinoma (8.0%) and bladder cancer (7.8%).

As for the efficacy of ICI therapy (1105 patients from MSK-IMPACT cohort), the OS of patients with MDM2/4 AMP (n=54) was obviously shorter than that of non-MDM2/4 AMP population (n=1051) (11 months vs 17 months, p=0.002) (figure 1A). Moreover, we observed that MDM2/4 AMP (with high TMB [TMB-H] or low TMB [TMB-L]) suggested the shortest OS as compared with higher levels of MSI (MSI-H) and non-MDM2/4 AMP (with TMB-H or TMB-L) (figure 1B). The TMB of patients with MDM2/4 AMP was substantially lower than that of those without the AMP (5.84 vs 12.15, p<0.001). One out of the 54 patients with MDM2/4 AMP had MSI-H. When TMB and MSI status was adjusted for a multivariable Cox regression analysis, MDM2/4 AMP was still an independent risk factor for identifying patients who did not benefit from ICI treatment (p=0.019; HR, 1.46; 95% CI 1.07 to 2.00).
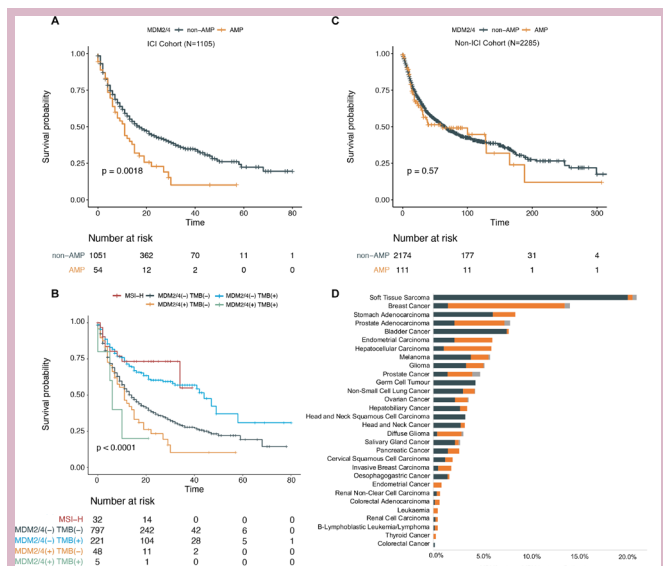
Figure 1 Overall survival (OS) of patients with MDM2/4 AMP versus those without MDM2/4 amplification (ICI cohort (A) and non-ICI cohort (C)). MDM2/4 AMP (with TMB-H or TMB-L) suggested the shortest OS as compared with higher levels of MSI and non-MDM2/4 AMP (with TMB-H or TMB-L) (B). (D) Prevalence of MDM2/4 amplification in 30 118 patients with different cancer types. AMP, amplification; ICI, immune checkpoint inhibitors; MSI, microsatellite instability; TMB, tumour mutational burden.

There was no significant difference in the OS after non-ICI treatment between MDM2/4 AMP and non-MDM2/4 AMP patients (figure 1C; 62 months vs 66 months, p=0.57), meaning that MDM2/4 AMP was a predictive biomarker of ICI therapy efficacy but not a prognostic biomarker.

DISCUSSION

This is the first large-scale systematic study focusing on the role of MDM2/4 AMP in ICI therapy. According to our result, MDM2/4 AMP was an indication of poor survival after ICI therapy. The application of MDM2/4 AMP screening before ICI treatment may help avoid delay of the effective treatment, adverse effect of ICI and financial burden without clinical benefit.

We hypothesised that the underlying mechanism may be that the MDM2/4 AMP population were largely TMB-L and lower levels of MSI. But MDM2/4 AMP was an independent negative predictor in the multivariable Cox regression, making the hypothesis above inconclusive. MDM2/4 are oncogenic through the inactivation of p53, a tumour suppressing transcription factor. Previous studies have confirmed that MDM2 can mediate the resistance to immunotherapy by reducing T cell activation in malignancies.[7 8] Immune normalisation alone seemed to be insufficient in the MDM2/4 AMP population. There have been some clinical trials about MDM2 antagonists, which may be an optimal choice for MDM2 AMP cancer patients in the future.

In conclusion, MDM2/4 AMP has the potential for being a negative pan-cancer biomarker for ICI therapy in different kinds of cancer. However, our study has several limitations. Due to the data restrictions, we did not include other factors that might influence the immunotherapy efficacy in the analysis. The number of patients with MDM2/4 AMP was limited, and further prospective studies are warranted to confirm the negative predictive role of MDM2/4 AMP in ICI therapy.

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