Hepcidin expression as a predictive biomarker for anti-PD1/PDL1 antibody monotherapy for advanced non-small cell lung cancer

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Background
- Immune checkpoint inhibitors (ICIs) have been a key therapeutic agents of advanced non-small cell lung cancer (aNSCLC).
- A previous study showed that CD68+ cell-promoted tumor ferrosis, a form of iron-induced cell death, is involved in the anti-tumor activities of ICIs. While malignant cells require high amounts of iron for proliferation, iron also facilitates the production of oxygen radicals, which may result in ferrosis.
- Hepcidin, a key regulator of iron metabolism, is overexpressed in kinds of cancer cells. Our previous study showed that hepcidin altered a T cell function. However, little is known about efficacy of ICIs on aNSCLC with hepcidin overexpression.
- The aim of this study is to examine efficacy of anti-PD1/PDL1 antibody monotherapy on aNSCLC patients with hepcidin overexpression tumor cells.

Methods
- This is a retrospective observational study. Among 108 of histologically confirmed aNSCLC patients in our previous study, who had history of nivolumab, pembrolizumab or atezolizumab monotherapy as any line of treatment from January 1, 2016, to August 24, 2018, eligible subjects with residual ferritin-immunofixed tumor samples for immunohistochemical stain (IHC) were selected.
- IHC for hepcidin (Hep) and interferon gamma (IFNg) was conducted with anti-Hepcidin-25 antibody ab30760 (Abcam) and anti-Interferon gamma antibody ab281426 (abcam, Cambridge, UK), respectively. Tissue proportion scores (TPS: High: >=50%, None and Moderate:1–49%) of Hep and IFNg were assessed by an experienced urologist.
- The Kaplan-Meier method was used to estimate time to progression (TTP).
- Statistical analysis was conducted using GraphPad Prism 9. Data cutoff was March 31, 2021.

Results
- Characteristics of 45 eligible subjects are shown in Table 1.
- Representative IHC results were shown in Figure 1. There was no significant difference in hepcidin TPS between historical types (Figure 2) or PDL1 TPS (Figure 3A).
- The median patient follow-up was 128 days (range, 18 to 1877 days).
- The median TTP was 264 days and 126 days for PDL1 TPS High (>= 50%) and None and Moderate, N/A (49.4 %), respectively. The HR and p value for disease progression were 0.90 (95% CI, 0.44 to 1.81) and p = 0.76 by log-rank test (Figure 3B).
- The median TTP was not reached (95% CI, N/A) and 126 days (95% CI, 53-273 days) for hepcidin High (>= 50%) and None and Moderate (49 %), respectively. (Figure 4)
- The hazard ratio (HR) and p value for disease progression with hepcidin High versus None and Moderate were 0.31 (95% CI, 0.13 to 0.78) and p = 0.087 by log-rank test. (Figure 4)

Conclusions
- aNSCLC patients with hepcidin TPS high may highly benefit from anti-PD1/PDL1 antibody monotherapy.
- Further evaluation with large numbers of cases is needed to explore the role of hepcidin as a predictive biomarker for anti-PD1/PDL1 antibody treatment.
- Similar observation study in other malignant may help to predict the efficacy of anti-PD1/PDL1 antibody.
- Features of cancer cells with increased expression of hepcidin must be explored besides influences of hepcidin on immune cells.

References

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