論　文　内　容　要　旨

Serum high-mobility group box 1 as a predictive marker for cytotoxic chemotherapy-induced lung injury in patients with lung cancer and interstitial lung disease

（間質性肺疾患合併肺癌患者における細胞障害性抗癌剤による薬剤性肺障害の予測マーカーとしてのHMGB1の有用性）

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I conducted this analysis to elucidate the predictive biomarker and the pathogenesis of cytotoxic chemotherapy-induced lung injury in patients with lung cancer and interstitial lung disease (ILD). As a result, I identified that higher serum levels of high-mobility group box 1 (HMGB1) could predict this life-threatening adverse event, and, additionally, ILD and higher tumor burden promoted disease development through increased circulatory HMGB1.

Cancer chemotherapy-induced lung injury is a life-threatening adverse event, and ILD is a well-known risk factor of the disease. In patients with lung cancer and ILD, the reported incidence rate of cytotoxic chemotherapy-induced lung injury ranges from 13.3% to 34.9%. However, the pathogenesis and predictive markers of this serious adverse event remain unclear.

HMGB1 is one of the damage-associated molecular patterns released by injured cells. HMGB1 binds to cell surface receptors, such as the receptor for advanced glycation end product (RAGE), and this interaction accelerates pro-inflammatory intracellular signaling associated with tumorigenesis and acute lung injury, which includes acute exacerbation of ILD. It was shown that HMGB1 was highly expressed in lung cancer tissue, and circulatory HMGB1 levels were shown to be increased by larger tumor size and decreased by surgical resection of the tumor. Additionally, a previous report showed that the presence of ILD elevated HMGB1 circulatory levels, and importantly, these higher levels at the baseline could predict earlier onset of acute exacerbation of ILD. Based on these observations, I hypothesized that the levels of circulatory HMGB1 would be increased in patients with lung cancer and ILD, and HMGB1 could be a predictive blood biomarker for cytotoxic chemotherapy-induced lung injury in these patients.

The present study included 83 consecutive advanced lung cancer patients with ILD and background-matched 83 patients without ILD from 743 patients who were diagnosed and treated at the Hiroshima University Hospital between October 2003 and December 2018. Additionally, 83 healthy subjects were included. After measuring baseline levels of serum HMGB1 in three groups, I evaluated the predictive values of baseline HMGB1 levels for cytotoxic chemotherapy-induced lung injury in patients with lung cancer and ILD.

As a result, twenty-five (30.1%) of patients with lung cancer and ILD experienced cytotoxic chemotherapy-induced lung injury within one year of starting cytotoxic chemotherapy. Serum levels of HMGB1 in lung cancer patients with ILD were significantly higher than in those without, and these levels were significantly higher than those among the healthy controls. Multivariate linear regression analysis revealed that higher levels of serum HMGB1 were independently associated with higher tumor burden, as assessed by total tumor size, and the presence of ILD in all study subjects. Univariate Cox proportional hazards model showed that higher levels of HMGB1 and higher tumor burden were

associated with disease onset. Moreover, multivariate analysis revealed that only HMGB1 was independently associated with this severe complication in patients with lung cancer and ILD.

These data indicate that the circulatory levels of HMGB1 play a promising role in the development of cytotoxic chemotherapy-induced lung injury in patients with lung cancer and ILD, and higher tumor burden may accelerate this severe complication via increasing circulatory HMGB1. Additionally, these data indicate that the presence of ILD could also promote the augmented pro-inflammatory condition in the lungs of lung cancer patients by increasing HMGB1 levels, which helps to explain the association between the presence of ILD and the risk of cytotoxic chemotherapy-induced lung injury.

In this study, I also evaluated serum levels of soluble receptor for advanced glycation end products (sRAGE) which acts as a decoy receptor for HMGB1 and inhibits HMGB1-associated inflammation, because our laboratory previously found that increased serum levels of sRAGE were associated with a reduced risk of acute exacerbation in patients with idiopathic pulmonary fibrosis. As a result, sRAGE higher levels were associated with reduced incidence of cytotoxic chemotherapy-induced lung injury in patients with higher levels of HMGB1. This data suggests that the effect of heightened HMGB1 could be canceled by high levels of sRAGE and support the hypothesis that HMGB1 is involved in the pathogenesis of chemotherapy-induced lung injury in patients with lung cancer and ILD.

In conclusion, this study suggests that the risk of cytotoxic chemotherapy-induced lung injury can be evaluated by measuring HMGB1 as a blood biomarker, and also suggests the potential pathogenesis of the disease; increased levels of HMGB1, which are derived from lung cancer and ILD, accelerates the lung injury. Because HMGB1 is a druggable molecular target by drug-repositioning, further investigations are needed to confirm this research results and to establish the preventative treatment for cytotoxic chemotherapy-induced lung injury based on the stratified risk by measuring serum HMGB1.