Poster

[P25-10] P25-10: Oncologic drugs (2)

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Mon. Sep 25, 2017 12:30 PM - 1:30 PM Annex Hall (1F)

(Mon. Sep 25, 2017 12:30 PM - 1:30 PM Annex Hall)

[P25-10-2] Molecular cornifing mechanisms of multi-targeted tyrosine kinase inhibitors-induced hand-foot skin reaction based on genetic differences of STAT3

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Keywords: multi-targeted tyrosine kinase inhibitor, STAT3, polymorphism, hand-foot skin reaction, keratinocyte

Background

Hand-foot skin reaction (HFSR) is a common side effect of multi-targeted tyrosine kinase inhibitors (mTKIs) causing dose reduction or interruption of therapy owing to its negative effect on quality of life. We found that the keratinocyte toxicity induced by mTKIs is contributed to the decrease of the levels of signal transducer and activator of transcription 3 (STAT3) phosphorylation. STAT3 is well known as a key regulator of cornification in skin, and its genetic polymorphisms are reported to affect functional differences of STAT3 in Japanese. In this study, we evaluated the association between development of HFSR and *STAT3* polymorphism in Japanese patients, and explored the cornification-related factors in molecular mechanisms of HFSR by microarray analysis based on the results of clinical study.

Methods

Renal Cell Carcinoma patients treated with mTKIs were retrospectively genotyped to elucidate a potential association between *STAT3* polymorphism rs4796793 and HFSR development. Microarray analyses were performed by using STAT3-knockdown keratinocyte and sunitinib-exposed 3D skin model.

Results

The final analysis included 60 patients, and HFSR was observed in 46 patients. A significant association was found between the GG and the GC + CC genotypes of rs4796793 (OR, 10.75; 95 % CI, 2.38-48.07; *P*= 0.001). In Kaplan-Meier analysis, a statistically significant difference was observed between the GG and the GC + CC genotypes in cumulative development of HFSR (*P*=0.009). Microarray analyses showed that some cornification-related genes showed higher or lower expression level in common with STAT3-knockdown keratinocytes and sunitinib-exposed 3D skin model compared with each control. Among proteins coded by these genes, an increase of filaggrin and keratin 5 expression, and a decrease of keratin 6 expression were demonstrated by immunohistochemistry using 3D skin model.

Conclusions

Our clinical and basic analyses indicate that genetic difference of *STAT3* may be a significant risk factor for mTKI-induced HFSR in Japanese patients, and cornification-related genes changing expression with the condition of STAT3-knockdown and the presence of mTKI may be important factors in molecular

pathological mechanism of HFSR.