

# **Bench-to-bedside research for the dermatological side effects induced by multiple tyrosine kinase inhibitors**

Kazuhiro Yamamoto

Department of Pharmacy, Kobe University Hospital  
Japan

## **Scope of the lecture:**

A large number of molecular targeted drugs have been used in clinical practice, and we are facing diverse adverse effects that we have not experienced previously. In particular, dermatological toxicity is frequently caused by various molecular targeted drugs, and this side effect often contributes interruption of therapy and decreases QOL in patients. Especially, the typical dermatitis induced by multiple tyrosine kinase inhibitor (mTKI), hand-foot skin reaction (HFSR), is a serious adverse reaction which affects therapeutic outcomes of mTKI, although pathological and molecular mechanisms of this reaction are unclear. This session summarizes our findings about the mechanisms of mTKI-induced dermatitis, risk factors of HFSR, and mechanism-based prophylaxis of HFSR in the bench-to-bedside research.

## **Learning objectives:**

1. To understand the method for approach from clinical question to practice of study.
2. To gain knowledge on the current various techniques to evaluate clinical toxicology.

## **Extended abstract:**

The cancer chemotherapy has led to significant advances by molecular targeted drugs. However, some safety and unique issues have emerged. In particular, adverse reactions induced by multiple tyrosine kinase inhibitors (mTKI) are some of the major causes for the interruption of therapy involving these drugs<sup>1)</sup>. Dermatological adverse events, also called hand-foot skin reaction, manifest topically in the palmar and plantar regions, and the pathological mechanism underlying these events is unclear. Because there are few treatment options for renal cell carcinoma and hepatocellular carcinoma, the success of therapy is determined by the length of efficient treatment and the management of adverse reactions. Therefore, appropriate management of the side effects will lead to an improvement in not only the quality of life, but also the outcome of therapy<sup>2, 3)</sup>. Although the dermatological adverse reactions induced by mTKIs are recognized as serious problems in clinical practice, a preventive method based on the pathological mechanism of these drugs has not been established.

We reported that the inhibition of signal transducer and activator of transcription 3 (STAT3) contributes to the mechanism for keratinocyte toxicity induced by mTKIs<sup>4)</sup>, and that the development of hand-foot skin reaction induced by mTKIs is associated with STAT3 polymorphisms<sup>5)</sup>. STAT3 is a well-known transcriptional factor that regulates cell growth, proliferation, inflammation, and apoptosis<sup>6)</sup>. Interestingly, STAT3 was reported to maintain homeostasis by regulating cell growth and differentiation in the skin<sup>7, 8)</sup>. It was also reported that psoriasis, characterized as epidermal hyperplasia, is associated with STAT3 activity<sup>9)</sup>. Therefore, STAT3 activity is theorized to be associated with various cutaneous disorders. Basically, the agent rescuing the STAT3 activity topically may be a prophylaxis for mTKI-induced dermatological side effects.

Vitamin C (VC) is essential for synthesizing collagen in human skin and its efficacy for activating skin turnover has been established in the field of cosmetics. Although the drawback of VC is its low permeability into epidermal skin, this problem was overcome by the recent

development of VC derivatives<sup>10</sup>. Especially, ascorbyl-2-phosphate magnesium (P-VC-Mg) has attracted attention, because it has high permeability to the subcutaneous tissue and high stability on the epidermal skin. Moreover, lipophilic VC was reported to be highly effective in scavenging oxidative stress and suppressing apoptosis compared to hydrophilic VC<sup>11</sup>. Interestingly, dehydroascorbic acid was also reported to induce the increase of STAT3 phosphorylation in cardiomyocytes<sup>12</sup>.

We evaluated the efficacy of the VC derivative P-VC-Mg on mTKI-induced keratinocyte toxicity. Analysis of the effects of P-VC-Mg on the sorafenib-induced apoptosis and pathological changes were performed using human keratinocyte cell lines and a 3D skin model. P-VC-Mg attenuates sorafenib-induced apoptosis in human keratinocytes mediated by the maintenance of STAT3 activity. We established a model for hand-foot skin reaction induced by sorafenib and demonstrated the effects of P-VC-Mg on the skin toxicity induced by sorafenib. P-VC-Mg has potential as a mechanism-based protective agent against hand-foot skin reaction.

This session will be introduced our findings about roles of STAT3 in the mechanisms of mTKI-induced dermatitis, risk factors of HFSR, and mechanism-based prophylaxis of HFSR in the bench-to-bedside research.

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