再発難治性骨髄腫の生物学とその治療

～耐性機序を含めて～

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KEY WORDS
●枝分かれ的
●耐性
●プロテアソーム変異
●セレブロン

Abstract

Novel agents including proteasome inhibitor and immunomodulatory drugs (IMiDs) have been widely used in the treatment of multiple myeloma (MM) both at untreated and relapsed settings. However, the mechanism of action of these drugs is poorly understood. Elucidating how these agents kill myeloma cells is indispensable to predict the response and adverse events of these agents, and to overcome drug resistance. We have focused on the action of two agents, bortezomib (BTZ) and lenalidomide (LEN), mostly used in Japan, and introduced cytotoxic mechanism of these agents precisely. Among actions of BTZ on MM cells, progression of endoplasmic reticulum (ER) stress followed by unfolded proteins response (UPR) has been considered to be the dominant pro-apoptotic pathway when proteasome function is inhibited. We also introduce a recent report that low expression of spliced XBP1, a key component of UPR, has emerged as the important mechanism of resistance against proteasome inhibitor via reduction of ER overload. As for LEN, cereblon (CRBN) was identified as a key mediator of IMiDs. It functions as an E3 ubiquitin ligase. Activation of this activity by LEN leads to degradation of IKZF1/IKZF3, which results in the inhibited transcription of IRF4, which is an essential factor for survival and proliferation of MM cells.

Biology of relapsed/refractory multiple myeloma.
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はじめに

近年，プロテアソーム阻害薬と免疫調整薬(immunomodulatory drugs；IMiDs)は，幅広く多発性骨髄腫(multiple myeloma；MM)の治療に使用されているもの，治癒に至る症例は限定的であり，多くは薬剤耐性を獲得し，治療抵抗性になっていく。このような再発性骨髄腫細胞が，どのような遺伝