



## Nagoya City University Academic Repository

学位の種類	博士 (医学)
報告番号	甲第1942号
学位記番号	第1372号
氏名	浅野 有彩
授与年月日	令和5年3月24日
学位論文の題名	Aberrant tryptophan metabolism leads to unfavorable outcomes in lenalidomide - treated myeloma patients (レナリドミド投与骨髄腫患者でのトリプトファン代謝異常の臨床的意義)  HematolOncol. 2022 Nov 25. doi: 10.1002/hon.3108. Online ahead of print.
論文審査担当者	主査： 山崎 小百合 副査： 高橋 智, 加藤 洋一

## Abstract

### [Background]

Multiple myeloma (MM) is a monoclonal plasma cell proliferative disorder. MM is characterized by a patchy infiltration into the bone marrow (BM). Recent studies show that the BM microenvironment plays an important role in survival, growth, drug resistance, and in immune escape of MM cells. Although development of a novel therapies has improved the prognosis of MM patients, MM still remains an incurable disease. Among several agents, Lenalidomide (Len) is a key drug for the treatment of MM. Its mechanisms of action have been recognized as not only the growth inhibitory effects on MM cells, but also immunomodulatory effects on a tumor immunity. Indoleamine 2,3 - dioxygenase 1 (IDO) is an enzyme that metabolizes tryptophan (Trp) to kynurenine (Kyn), and considered as an important factor in a suppression of tumor-specific T cells . Here, we investigated the clinical impact of aberrant Trp metabolism in MM patients treated with Len and evaluated its effects on T cell immunity *ex vivo*.

### [Methods]

In our study, 72 patients with relapsed or refractory (RR) MM received Len plus dexamethasone (Ld) therapy were evaluated. Kyn and Trp concentrations in sera from patients collected prior to Ld therapy were measured. Associations of the Kyn/Trp ratio with progression - free survival (PFS) and overall survival (OS) were analyzed. Next, the expressions of IDO in MM and stromal cells were evaluated with or without co-culture. Finally, activation of T cells were compared between culture mediums with several Kyn/Trp ratio in the presence or absence of Len treatment.

### [Results]

Patients with high serum Kyn/Trp ratios ( $\geq 46.0$ ,  $n = 22$ ) had significantly shorter PFS and OS than those with low ratios (4.9 vs. 12.6 months, and 15.5 vs. 45.7 months, respectively). MM cells promoted IDO expression in stromal cells during co - culture in both a direct contact and an indirect manner. Incubation in medium with a high Kyn/Trp ratio significantly inhibited T cell cytokine production and upregulated the expression of inhibitory immune receptors. These effects were sustained even in the presence of Len.

### [Conclusions]

A high serum Kyn/Trp ratio is associated with poor prognosis in patients with MM. We propose that aberrant Trp metabolism reduces anti - tumor immunity and the efficacy of Len therapy.