論文の内容の要旨

論文題目　A clinical study of hypoplastic myelodysplastic syndrome
(a nationwide multicenter retrospective study)
（低形成性骨髄異形成症候群の臨床病態に関する研究（全国多施設後方視的研究））

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Hypoplastic MDS (hMDS) is a new disease entity characterized by bone marrow hypocellularity and dysplasia, and because of the risk of death from bone marrow failure (BMF), adequate treatment strategies for hMDS are still unknown. This study is intended to elucidate the clinical characteristics and adequate treatments of hMDS by nationwide retrospective clinical research.

The data of 143 hMDS patients, diagnosed between April 2003 and March 2012, were collected from 21 institutions and the central review team of the Idiopathic Disorders of Hematopoietic Organs Research Committee, and compared with the data of 143 non-hMDS patients.

Comparing the backgrounds of hMDS and non-hMDS patients at initial diagnosis, more RA and fewer CMMoL and RAEB-t were found in hMDS than non-hMDS in French-American-British (FAB) classification, and more RCUD and MDS-U patients and fewer RCMD patients were found in World Health Organization (WHO) classification with statistically significant differences. Also, the patients with family histories of hematological diseases and/or malignancies and the patients with smoking habits were significantly fewer in hMDS than non-hMDS. However, no significant differences were found in International Prognostic Scoring System (IPSS) and revised IPSS (IPSS-R).

The 5-year overall survival (OS) and acute myeloid leukemia progression-free survival (AML-PFS) of hMDS were 62% (95% confidence interval (C. I.) = 51-76%) and 61% (95% C. I. = 50-74%), respectively. The 5-year OS and AML-PFS of hMDS at age <50 were higher than those at age ≥50 (94% versus 64% (P=0.10), and 94% versus 59% (P=0.041), respectively). The lower risk groups of IPSS (low and intermediate-1) exhibited significantly higher 5-year OS and AML-PFS than higher risk groups of IPSS (intermediate-2 and high) (77% versus 31% (P<0.001), 80% versus 24% (P<0.001), respectively). Likewise, the lower risk groups of IPSS-R (very low, low and intermediate) exhibited significantly higher 5-year OS and AML-PFS than higher risk groups of IPSS-R (high and very high) (88% versus 8.1% (P<0.001), and 88% versus 7.3% (P<0.001), respectively).

The 5-year OS and AML-PFS of hMDS were higher than those of non-hMDS (62% versus 52% (P=0.094), and 61% versus 52% (P=0.013), respectively), which were attributed to hMDS at age <50 (94% versus 64% (P=0.10), and 94% versus 59% (P=0.041), respectively) and hMDS of lower risk

groups in IPSS (low and intermediate-1) (77% versus 58% (P=0.066), and 80% versus 50% (P=0.0036), respectively) and IPSS-R (very low, low and intermediate) (89% versus 62% (P=0.0073), and 90% versus 54% (P<0.001), respectively). The OS and AML-PFS between hMDS and non-hMDS for age ≥50, higher risk groups of IPSS (intermediate-2 and high) and IPSS-R (high and very high) did not exhibit statistically significant differences.

The risks of hMDS to progress to acute myeloid leukemia (AML) and to die from BMF were analyzed by competing risks analysis. The hMDS patients exhibited lower risk of AML-progression than non-hMDS patients, with the 5-year cumulative incidence of 18% and 30%, respectively (P=0.0074). Furthermore, no hMDS patients at age <50 progressed to AML while some non-hMDS patients progressed to AML, with the 5-year incidence of 0% and 22%, respectively (P=0.057), and hMDS patients in lower risk groups of IPSS (low and intermediate-1) exhibited significantly lower risk of AML-progression than non-hMDS patients in lower risk groups of IPSS, with the 5-year cumulative incidence of 6.2% and 27%, respectively (P=0.0027). Likewise, hMDS patients in lower risk groups of IPSS-R (very low, low and intermediate) exhibited significantly lower risk of AML-progression than non-hMDS patients in lower risk groups of IPSS-R, with the 5-year cumulative incidence of 5.9% and 25%, respectively (P=0.0025). The hMDS patients exhibited significantly higher risk of death from BMF than non-hMDS, with the 5-year cumulative incidence of 20% and 5.7%, respectively (P=0.0086). No patients at age <50, both hMDS and non-hMDS, died from BMF, but the hMDS patients at age ≥50 exhibited significantly higher risk of death from BMF than non-hMDS patients (5-year cumulative incidence: 23% versus 7.2% (P=0.011)). Also, the hMDS patients' higher risk of death from BMF was attributed to high and very high risk groups in IPSS-R when compared with non-hMDS patients in the higher risk groups of IPSS-R (5-year cumulative incidence: 51% versus 17% (P=0.039)).

Cox proportional hazards models revealed that poor performance status (PS ≥2) and high karyotype risks in IPSS-R (poor and very poor risk groups) were significant risk factors of death and progression to AML for hMDS patients as well as non-hMDS patients and all patients, in both univariate and multivariate analyses. Also, for hMDS patients, past illnesses of malignancies and/or hematological diseases and smoking were significantly significant risk factors for death and AML-progression in univariate analysis, and male gender was a significant risk factor for death and AML-progression in both univariate and multivariate analyses.

A subset analysis of histology-proven hMDS was performed to confirm that the study including patients diagnosed without bone marrow biopsy still represents the characteristics of histology-proven hMDS, and it was confirmed by Kolmogorov-Smirnov analysis that both histology-proven hMDS and the other hMDS follow the same distributions in most of the background variables at initial diagnosis.

The OS of patients according to their initial treatments were also analyzed, but the OS between hMDS and non-hMDS did not exhibit statistically significant differences in any treatment, partly due to the limited sample sizes. In order to investigate adequate treatment choices for hMDS, however, a study

with even a larger size of population is required.

The subset analysis of patients both at age <50 and in lower risk groups of IPSS-R (very low, low and intermediate) was performed. The hMDS patients of this subpopulation neither died nor progressed to AML, and no patients, both hMDS and non-hMDS, died from BMF.