

Treatment outcomes and prognostic factors in adult patients with secondary hemophagocytic lymphohistiocytosis not associated with malignancy

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Supplemental methods

Identification of the causes of HLH

UNC13D and PRF1 gene mutation was checked in patients younger than 30 years old for identification of primary HLH. Associated causes of HLH were thoroughly assessed by laboratory tests and imaging tools to identify malignant disease, autoimmune disease, and infectious diseases including EBV infection. Whole body computed tomography (CT) scans were performed in almost all patients to find out possible malignancies. After 2009, positron emission tomography (PET)-CT was frequently used. However, for some cases we were unable to identify the cause of HLH. EBV-association was evaluated by serologic tests using EBV early antigen (EA) and nuclear antigen (EBNA) and viral capsid antigen (VCA) IgG/IgM before 2006, and both serology and EBV DNA RQ-PCR were used after 2006. We defined recent primary infection of EBV when both VCA-IgG/IgM and EA are positive, and reactivation when both VCA-IgG/IgM and EBNA are positive, and past infection when only VCA-IgG and EBNA are positive. EBV-specific RQ-PCR was performed with an Artus EBV LC PCR kit (QIAGEN) and a LightCycler 1.5 (Roche Diagnostics, Mannheim, Germany). Some BM biopsy samples were evaluated by EBV-encoded-RNA (EBER) *in situ* hybridization.

Statistical analysis

All categorical variables were compared by Fisher's exact test and continuous variables were assessed by the Mann-Whitney *U* test for comparisons between two groups. We used receiver operation characteristic (ROC) curve analysis to determine the cut-off levels for continuous variables for predicting death or disease progression. Overall survival (OS) rates were calculated using the Kaplan-Meier method, and log-rank analysis was used to evaluate differences between subgroups. Patients who received allogeneic HCT after progression were censored at the time of transplantation. Cumulative incidence of progression (CIP) was calculated by cumulative incidence estimation treating non-relapse deaths as competing risks and the results were compared using the Gray test. Multivariate analyses by Cox's proportional regression model were used to calculate the survival hazard ratio. All statistical analyses were performed using the Statistical Package for Social Sciences,

version 14.0 (SPSS Inc., Chicago, IL, USA). Cumulative incidence analyses were carried out with 'R' software version 2.15.1 (R Foundation for Statistical Computing, 2012). Statistical significance was set at a p -value < 0.05 .