学位論文内容の要旨

博士の専攻分野の名称：博士（獣医学）　　氏名：金 尚昊

学位論文題名

Allogeneic peripheral blood stem cell transplantation using nonmyeloablative pretransplant conditioning regimen in dogs

（犬における骨髄非破壊的前処置を用いた同種末梢血幹細胞移植に関する研究）

Lymphoma is the most common canine hematopoietic tumor. Although various chemotherapeutic protocols for canine lymphoma have been reported, treatment outcomes have remained static for several decades. Hematopoietic stem cell transplantation (HSCT) has been used as a critical therapy for human hematologic malignancies. In past decades, canine HSCT has been investigated as a preclinical model for human patients, and there are only a few reports in the literature on whether those conditions are actually applicable for canine cancer patients.

In chapter I, to investigate the effective mobilization protocols for collecting the required number of peripheral blood $CD34^+$ stem cell (PBSC) from the recipient, this study performed stem cell mobilization using high-dose plerixafor alone, a granulocyte-colony stimulating factor (G-CSF) alone, or the combination of the plerixafor and G-CSF. The Spectra Optia® continuous mononuclear cell protocol was used in all apheresis procedures. Three healthy dogs were assigned to each mobilization protocol. Regardless of the mobilization protocol, the apheresis procedures were uniformly set as the same condition, and the numbers of PBSCs within the apheresis product were compared. The mean PBSC counts of the apheresis products for plerixafor, G-CSF, and the combination group were 1.3 ± 0.24, 4.2 ± 0.47, and $6.4 \pm 0.9 \times 10^6$ cells/kg, respectively. PBSC mobilization with a combination of G-CSF and plerixafor appeared to be the most effective protocol among the three protocols.

In chapter II, to establish a safe and effective pretransplant conditioning treatment for the donor dog, this study evaluated the feasibility of total lymphoid irradiation (TLI) with volumetric modulated arc therapy (VMAT) as a nonmyeloablative HSCT conditioning method. Six healthy dogs were treated with 8 or 12 Gy TLI using VMAT. To assess the effect of the peripheral lymphocyte condition, the lymphocyte subset, and proliferation ability were examined. In addition, allogeneic HSCT was performed in dog leukocyte antigen-identical littermates using 12 Gy TLI. After HSCT, the recipient was administered two immunosuppressive drugs. Chimerism analysis with a microsatellite marker was performed at 16 weeks to evaluate the engraftment. All dogs demonstrated mild-to-moderate neutropenia and thrombocytopenia, and these hematologic changes recovered spontaneously. In one dog treated with 8 Gy TLI, transient cutaneous infection developed. Treatment in the other seven dogs did

not lead to any severe complications during the experimental period. In the allogeneic HSCT experiment, the recipient dog did not show any serious side effects before or after the transplantation. The chimerism was detected in the second week after transplantation and maintained until 16 weeks after transplantation. These results indicate that TLI with VMAT is a feasible nonmyeloablative treatment and might be useful for canine allogeneic HSCT conditioning.

The present study shows that PBSC apheresis and TLI with VMAT are feasible procedures for use in the veterinary field. In addition, the present study suggests that these procedures have the potential as an efficacious protocol for providing safe HSCT therapy in canine cancer patients.