Diminished T-cell recovery after CD34+ selected autologous peripheral blood stem cell transplantation increases the risk of cytomegalovirus infection

There are reports of a correlation between poor T-cell reconstitution and an increased risk of cytomegalovirus (CMV) reactivation in CD34+-selected autologous peripheral blood stem cell transplantation (CD34+-APBSCT). We reinforce this concept, and the possibility that pre-emptive therapy can prevent the occurrence of CMV disease after CD34+-APBSCT is discussed.

At the Hospital of Hokkaido University School of Medicine, Japan, 35 CMV-seropositive Japanese patients underwent a myeloablative conditioning regimen followed by APBSCT. Eleven patients (seven men and four women, median age 48 years) were found suitable for CD34+-APBSCT: they had non-Hodgkin's lymphoma (NHL) with bone marrow or cutaneous/subcutaneous involvement at presentation (n=9), or high-risk breast cancer (BC) (n=2). The group receiving unselected APBSCT included 24 patients (fifteen men and nine women, median age 51 years) with NHL (n=14), BC (n=1), multiple myeloma (MM) (n=7), Hodgkin's disease (n=1) or rhabdomyosarcoma (n=1). Since two patients with MM were twice given high-dose therapy with APBSCT, 26 courses were counted for the control.

CD34+ cells were positively selected using the Isolex Magnetic Cell Separation System (Isolex 50; Baxter Healthcare, Immunotherapy Division, Newbury, UK), as described elsewhere.[1,2] After selection, the median purity and number of CD34+ cells was 98.0% (range 95.2 to 99.4%) and 2.55×10^6/kg (range 1.07 to 4.71×10^6/kg), respectively. The number of CD34+ cells was not statistically different from findings in unselected patients (the median 3.15×10^6/kg, range 1.76 to 8.15×10^6/kg). There were no significant differences in the background of the two groups concerning age, the number of prior courses of chemotherapy or post-transplant steroids. Three patients in the CD34+-APBSCT group underwent a total body irradiation (TBI) - based regimen, while the 32 others were prescribed high-dose chemotherapy without TBI as their preconditioning regimen. CMV screening studies were done using the CMV antigenemia assay.[3] Testing was carried out weekly from day 14 until day 100. Patients with positive CMV antigenemia were promptly prescribed ganciclovir 5 mg/kg every 12 hours.

Eight of the 11 patients (72.7%) treated with CD34+-APBSCT developed CMV infection at a median of 25 days after transplantation. Of the 26 patients receiving an unselected APBSCT, only two (7.7%) developed CMV infection. The incidence of CMV infection was significantly higher in the CD34+-APBSCT group ($p = 0.0002$, Mann-Whitney U test) (Table 1). No patient in either group died of CMV infection. The numbers of CD3+ and CD4+ cells in the CD34+-APBSCT group decreased just after transplantation and were significantly lower than in the unselected APBSCT group during the 8 weeks following transplantation (Table 2). Two weeks after transplantation the number of CD8+ cells was markedly lower in the CD34+-APBSCT group than in the unselected APBSCT group. Contrasting with the T-cell subsets, the numbers of CD19+ B and CD56+ NK cells did not differ between the two groups (data not shown).

Holmberg *et al.*[4] reported a 22.6% incidence of CMV disease, with 4 of 7 patients who developed the disease dying of CMV infection, among patients undergoing CD34+-APBSCT. This high mortality suggested that any potential therapeutic gains from the CD34+-APBSCT would be diminished by the risk of CMV infection. However, in their study, only patients with antigenemia exceeding 5 cells/slide received antiviral therapy. Optimal prophylactic or pre-emptive treatment strategy for CMV disease with antigenemia after CD34+-APBSCT has not been established. Because the fatality rate of CMV pneumonia in autologous graft recipients is said to be comparable to that in allogeneic patients,[5,6] we treated all patients with any level of positive CMV antigenemia in an attempt to prevent pneumonia from occurring. This may explain why no patient in our series died of CMV disease. Since a higher incidence of CMV disease in MM patients undergoing autologous transplantation was reported, our patient selection, which did not include subjects with MM in the CD34+-APBSCT group, may be another explanation.[4,7]

There was a delayed recovery of T-cells in the CD34+-APBSCT group compared with findings in the unselected group, as previously reported.[8-10] In the present study, CMV infection after CD34+-APBSCT was documented at a median of 25 days after transplant. In another report, CMV disease occurred at a median of 26 days.[4] A decrease of T-cells in the first 3 weeks follow-

Table 1. Clinical characteristics of patients with CMV infection.

	Antigenemia			
Disease	*Days post-transplant*	*Positive cells/tested cells*	*Symptoms of CMV infection*	*Response to ganciclovir*
CD34+-selected				
NHL	32	1/43,000	fever, diarrhea, liver dysfunction	Yes
NHL	21	5/66,000	fever, liver dysfunction	Yes
	67	1/31,000	fever, liver dysfunction	Yes
NHL	18	1/42,000	fever, diarrhea	Yes
NHL	42	1/39,000	fever, liver dysfunction, thrombocytopenia	Yes
NHL	26	4/49,000	fever, SOB, thrombocytopenia	No*
BC	25	1/44,000	symptom free	Yes
NHL	11	1/36,000	fever	Yes
NHL	21	3/28,000	symptom free	Yes
Unselected				
MM	30	2/34,000	fever, thrombocytopenia	Yes
NHL	25	1/44,000	fever	Yes

*Abbreviations: NHL, non-Hodgkin's lymphoma; BC, breast cancer; MM, multiple myeloma; SOB, shortness of breath; *this patient had CMV-related pneumonia and was treated with foscarnet and methylpredonisolone pulse therapy.*

Table 2. Number and pattern of lymphocytes recovery after APBSCT.

	CD34+-selected	Unselected
CD3 (/μL)		
Before transplantation	808.7±362.0	638.4±355.2
Week 2	219.8±319.5*	677.7±387.8
Week 3	221.1±273.0*	923.2±536.0
Week 4	727.7±523.4*	1580.9±1038.7
Week 8	740.9±579.4*	2140.0±1716.8
Week 12	1072.5±515.4	1596.2±760.8
CD4 (/μL)		
Before transplantation	421.6±248.8	353.0±286.6
Week 2	104.9±133.0*	370.6±350.3
Week 3	102.4±184.7*	307.6±178.9
Week 4	185.1±171.9	344.7±217.8
Week 8	166.0±160.3*	358.7±77.7
Week 12	233.4±144.1	429.6±220.4
CD8 (/μL)		
Before transplantation	386.6±180.8	284.4±118.5
Week 2	130.3±250.4*	367.8±220.3
Week 3	162.9±124.1	667.4±807.4
Week 4	549.7±435.5	1264.7±1025.9
Week 8	637.1±409.8	1816.1±1560.4
Week 12	785.6±525.5	1212.9±815.8

**p<0.05: Decrease compared with the value for the unselected group. (Mann-Whitney U test).*

ing transplantation may perhaps be linked to increased rates of CMV infection in cases of CD34+-APBSCT.

As immunodeficiency is present, especially during the first 3 weeks after transplantation, and the incidence of CMV infection is high, we recommend that ganciclovir be prescribed as soon as CMV antigenemia is detected.

Mitsufumi Nishio, Kazuki Koizumi, Tomoyuki Endo, Katsuya Fujimoto, Takao Koike, Ken-ichi Sawada

Department of Internal Medicine II, Hokkaido University, School of Medicine, Sapporo, Japan

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Correspondence: Mitsufumi Nishio, M.D., Department of Internal Medicine II, Hokkaido University School of Medicine, N-15, W-7, Kita-ku, Sapporo 060-8638, Japan. Phone: international +81-11-7161161 (ext. 5915) – Fax: international +81-11-7067710 – E-mail: m-nishio@fc4.so-net.ne.jp

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