## Conclusion

We have reported an unusual case of EBV-negative, T-cell PTLD as γδ T-cell LGLL of donor origin after a second cord blood transplantation. The occurrence of T-cell PTLD after HSCT is extremely rare, and the efficient accumulation of knowledge and further research are needed to establish the oncogenic mechanism and appropriate therapeutic maneuvers in this disease entity.

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## Abdominal Pain and Syndrome of Inappropriate Antidiuretic Hormone Secretion as a Manifestation of Visceral Varicella Zoster Virus Infection in a Patient With Non-Hodgkin's Lymphoma

*To the Editor:* Lesions of varicella zoster virus (VZV) disease are usually limited to a few dermatomes. However, in immunocompromised patients, disseminated cutaneous and visceral involvement occurs. We report here a rare case of such a disseminated disease with manifestation of severe abdominal pain and syndrome of inappropriate anti-diuretic hormone (SIADH), which occurred 2 months after completion of conventional chemoradiotherapy for non-Hodgkin's lymphoma (NHL).

A 65-year-old woman was diagnosed as having diffuse large B-cell lymphoma of stomach origin. The clinical stage was II1 by the Lugano classification, and the International Prognostic Index score was low. HIV test was negative. She received chemotherapy consisting of three cycles of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP), followed by radiation at a total of 40.5 Gray to the involved field, and a complete response was obtained. Two months later, she was re-admitted to our hospital because of severe abdominal pain lasting 2 days.

Her vital signs and physical examination were normal. Laboratory examination revealed prominent hyponatremia (Na 122 mmol/l, normal 138–146) and mild liver injury (GOT 74 U/L, normal 13–33; and GPT 63 U/L, normal 6–27). The serum osmolarity was 262 mOsm/kg, and urine osmolarity 532 mOsm/kg, which was consistent with SIADH. The pituitary size and intensity was normal but the occipital lobe of the cerebrum showed a high intensity on brain magnetic resonance imaging. In spite of fluid restriction, hyponatremia and her pain deteriorated. On the sixth hospital day, a subtle vesicular skin lesion on her abdominal wall was observed. We reasoned that her complaint might be attributed to the visceral involvement of VZV extending to the peritoneum, liver, brain, and skin. Upon starting treatment with acyclovir at 1,500 mg/day, her abdominal pain and hyponatremia improved, and she was discharged on the 14th hospital day. Polymerase chain reaction (PCR) for VZV of her peripheral blood and cerebrospinal fluid taken before acyclovir therapy was later found to be positive. The number of CD4-positive lymphocytes was 191/$\mu$L, and this low level has been maintained for as long as 1 year. The complete remission of NHL was also maintained throughout the episodes.

The occurrence of disseminated VZV including visceral involvement has been limited to immunocompromised patients; after stem cell transplantation (SCT), ~17–50% of cases develop VZV infection [1,2], and, among them, visceral infection is rare (3.6% [2]). Especially, there are only a few VZV infection cases after SCT consisting of SIADH [3]. And only one case has been reported which developed along with severe abdominal pain and SIADH after conventional chemotherapy [4].

Storek et al. reported that the CD4-positive lymphocyte count after allogeneic SCT was inversely correlated with the infection score [5]. We suppose that her low CD4 count might have contributed to the visceral VZV infection. The reason why she showed such a low CD4 cell count is currently unknown.

It should be noted that this rare manifestation could occur even after conventional chemotherapy in NHL patients. Importance of recognition of this manifestation should be stressed because it is critical for the prompt diagnosis of the disease and its successful treatment.

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# Unrelated-Donor Bone Marrow Transplantation with a Conditioning Regimen Including Fludarabine, Busulfan, and 4 Gy Total Body Irradiation

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**Abstract**

We investigated the feasibility of reduced-intensity conditioning with 4 Gy total body irradiation, fludarabine (30 mg/m$^2$ for 6 days), and busulfan (4 mg/kg for 2 days) for bone marrow transplantation from a serologically HLA-matched unrelated donor. Seventeen adult patients (median age, 55 years; range, 27-67 years) with various hematologic malignancies (6 in remission, 11 not in remission) were treated. Successful engraftment was achieved in all patients at a median of day 18 (range, day 14-35) after transplantation, although subsequent secondary graft failure was observed in 2 patients. The cumulative incidence of acute graft-versus-host disease (GVHD) of grades II to IV at day 100 was 48%. With a median follow-up of 286 days (range, 56-687 days), the rates of 1-year overall survival, 100-day nonrelapse mortality, and 1-year nonrelapse mortality were 41%, 14%, and 46%, respectively. Eleven patients died, and the causes of death were relapse (n = 4), pulmonary complications (n = 4), acute GVHD (n = 2), and sepsis (n = 1). The remaining 6 patients (at transplantation, 2 were in remission, and 4 were not in remission) are currently still in remission. These results suggest that this regimen reduces the risk of graft failure, but further studies are needed to ameliorate transplantation-related toxicities, primarily GVHD and/or pulmonary complications.

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*Key words:* Unrelated donor bone marrow transplantation; Fludarabine; Busulfan, TBI

## 1. Introduction

Although allogeneic hematopoietic stem cell transplantation (HSCT) is a possible curative approach for patients with various hematologic malignancies, only 30% to 40% of patients in Japan have an appropriate family donor available [1]. Hence, the application of unrelated-donor transplantation using bone marrow or cord blood cells has been expanding. Another area of current interest is the application of reduced-intensity conditioning regimens, mostly incorporating fludarabine as a primary agent, because conventional allogeneic HSCT using a conditioning regimen with high doses of systemic chemotherapy/radiation is associated with significant toxicities. In contrast, HSCT with a reduced-intensity conditioning regimen allows older patients and those who have contraindicating comorbidities to undergo HSCT [2-7].

Nevertheless, special consideration should be paid to developing reduced-intensity conditioning protocols for the unrelated-donor HSCT setting, because the incidences of both graft rejection and graft-versus-host disease (GVHD) are greater than in related-donor transplantation. In addition, the intensity of the reduced-intensity conditioning regimen influences transplantation-related toxicities and the relapse rate, and the stem cell source (ie, peripheral blood stem cells or bone marrow cells) influences engraftment [8]. Accordingly, several reduced-intensity conditioning protocols have been tested to address a variety of problems [8-17]. In this study, we investigated the feasibility of bone marrow transplantation (BMT) from a serologically HLA-matched unrelated donor with a regimen containing

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4 Gy of total body irradiation (TBI), fludarabine (Flu), and busulfan (BU).

## 2. Patients and Methods

### *2.1. Patients and Donors*

The data for adult patients with hematologic malignancies who underwent unrelated-donor BMT through the Japan Marrow Donor Program between June 2002 and December 2003 at the National Cancer Center Hospital were analyzed retrospectively. This protocol was approved by the Ethics Committee, and written informed consent was obtained from each patient. The patients who were enrolled in this study were ineligible for conventional allogeneic HSCT because of age (older than 50 years) and/or concomitant diseases or preceding intensive therapies, such as autologous HSCT or multiple chemotherapies. Donor-recipient pairs were selected on the basis of serologic matching for HLA-A and HLA-B and molecular matching for HLA-DRB1. HLA allele typing was performed by intermediate-resolution polymerase chain reaction (PCR) analysis. The stem cell source, which was determined by the Japan Marrow Donor Program donor center, was bone marrow in all cases.

### *2.2. Treatment Plan and Evaluations*

The conditioning regimen consisted of 30 mg/m$^2$ Flu intravenously daily for 6 days (day –8 to day –3), 4 mg/kg BU orally daily for 2 days (days –6 and –5, without BU dose adjustment), and 4 Gy TBI without lung shielding (day –9 or day –1, single dose or 2 divided doses). Non–T-cell–depleted bone marrow was infused on day 0. The time of neutrophil engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count $\geq 0.5 \times 10^9$/L, and the time of platelet engraftment was defined as the first of 7 consecutive days with a platelet count $\geq 20 \times 10^9$/L without transfusion support. Granulocyte colony-stimulating factor (G-CSF) was administered at 300 μg/m$^2$ from day 6 and continued until neutrophil engraftment. The degree of donor chimerism among peripheral blood mononucleated cells was evaluated by PCR analysis of short tandem repeat polymorphisms with fluorescently labeled primers. Secondary graft failure was defined as cytopenia with an absolute neutrophil count $< 0.1 \times 10^9$/L or decreasing chimerism not associated with relapsing disease in patients who had recovered in the early posttransplantation period.

GVHD prophylaxis consisted of cyclosporin A (CsA) from day –1 (daily administration of 3 mg/kg by continuous intravenous infusion or 6 mg/kg orally in 2 divided doses) and methotrexate (10 mg/m$^2$ intravenously on day 1 and 7 mg/m$^2$ on days 3, 6, and 11). The CsA dosage was adjusted according to the patient's renal function and to maintain therapeutic levels (250-350 ng/mL) with continuous infusion or trough levels (150-250 ng/mL) with oral administration. In patients without GVHD, CsA was tapered from day 100 over a 3- to 6-month period. Standard criteria were used to grade acute and chronic GVHD [18,19]. Chronic GVHD was evaluated in patients who survived at least 100 days and was classified as limited or extensive. Patients who developed acute GVHD ≥grade II were treated with methylprednisolone at 1 to 2 mg/kg per day.

### *2.3. Supportive Care*

Antimicrobial prophylaxis consisted of ciprofloxacin, fluconazole, acyclovir, and trimethoprim/sulfamethoxazole according to our institutional protocol. All patients were nursed in a room equipped with high-efficiency air filtration of particulates. Monitoring for cytomegalovirus (CMV) antigenemia was performed once a week after neutrophil engraftment by means of the horseradish peroxidase–C7 method. Patients positive for CMV antigenemia were started preemptively on ganciclovir therapy.

### *2.4. Statistical Analysis*

Overall survival was calculated from the time of transplantation until death from any cause. Progression-free survival was measured from transplantation until disease progression or death from any cause. Nonrelapse death was defined as death due to any cause other than relapse. Survival curves for overall survival and progression-free survival were estimated by the Kaplan-Meier method.

## 3. Results

### *3.1. Patients*

The median age of the 17 patients was 55 years (range, 27-67 years; Table 1). The diagnoses were acute myeloid leukemia (AML) (n = 7), myelodysplastic syndrome (MDS) (n = 4), chronic myelogenous leukemia (n = 1), non-Hodgkin's lymphoma (n = 4), and multiple myeloma (n = 1). Six patients were in remission at transplantation, and the remaining 11 were not in remission. Three patients with MDS or AML following MDS underwent unrelated-donor BMT as a primary treatment. Seven donor-recipient pairs were fully matched for HLA-A, HLA-B, and HLA-DRB1 at the allele level, 4 donor-recipient pairs had an allele-level mismatch at the HLA-A locus, and 5 pairs had an allele-level mismatch at the HLA-DRB1 locus. One patient was mismatched with the donor at 3 HLA alleles.

### *3.2. Engraftment and Chimerism*

The median number of infused nucleated cells was $2.7 \times 10^8$/kg (range, $0.65\text{-}5.5 \times 10^8$/kg). All patients achieved neutrophil recovery, but 5 patients did not become independent of platelet transfusion during their follow-up period (Table 2). The median times until neutrophil and platelet recoveries were 18 days (range, 14-35 days) and 26 days (range, 15-112 days), respectively (Figure 1). Late graft failure was observed in 2 patients, one of whom had secondary graft failure due to myelosuppression caused by ganciclovir treatment for CMV colitis. In this patient, donor chimerism was not assessed after day 30 when complete donor chimerism was confirmed. In the other case, donor chimerism decreased from 89% on day 30 to 33% on day 60, despite the tapering of CsA from day 30. Chimerism was

**Table 1.**
Patient and Disease Characteristics*

| Patient No. | Age, y/Sex | Disease | Status | Time from Dx to HSCT, mo | HLA Allelic Mismatch | GVH Vector | HVG Vector | Contraindications to Conventional HSCT | Pretransplantation Comorbidities |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 55/F | AML | CR3 | 117 | | | | Age | No |
| 2 | 52/F | AML | Primary Ref | 13 | DRB1 | 1 | 1 | Age + comorbidity | Pneumonia |
| 3 | 57/F | AML | Rel2 | 28 | | | | Age | Atrial fibrillation |
| 4 | 55/M | MDS | Primary Ref | 3 | | | | Age | Atrial fibrillation |
| 5 | 57/M | MDS | CR1 | 8 | | | | Age | No |
| 6 | 59/M | CML | CP2 | 8 | | | | Age | No |
| 7 | 55/M | PTCL | PR | 16 | DRB1 | 1 | 1 | Age | Gastric ulcer |
| 8 | 58/M | AML | Untreated | 10 | DRB1 | 1 | 1 | Age | Bronchial asthma, $FEV_1$ 75% |
| 9 | 59/M | AML | Untreated | 33 | DRB1 | 1 | 1 | Age | Bilirubin 1.5 mg/dL |
| 10 | 52/M | AML | CR1 | 11 | A | 1 | 1 | Age | $FEV_1$ 67% |
| 11 | 57/M | MDS | CR1 | 13 | | | | Age | Prior gastric cancer |
| 12 | 61/M | AML | CR2 | 58 | A, both DRB1 | 3 | 3 | Age | No |
| 13 | 67/F | FL | Primary Ref | 58 | A | 1 | 1 | Age + comorbidity | Dyspnea requiring oxygen |
| 14 | 27/M | DLBCL | Rel3 | 38 | A | 1 | 0 | Prior autologous HSCT | No |
| 15 | 48/F | MM | Primary Ref | 80 | | | | Comorbidity | Ventricular septal defect |
| 16 | 52/F | MDS | Untreated | 130 | A | 1 | 1 | Age | No |
| 17 | 49/M | FL | Rel1 | 28 | DRB1 | 1 | 1 | Prior multiple chemotherapies | No |

*Dx indicates diagnosis; HSCT, hematopoietic stem cell transplantation; GVH, graft-versus-host; HVG, host-versus-graft; AML, acute myeloid leukemia; CR3, third complete remission; Ref, refractory; Rel2, second relapse; MDS, myelodysplastic syndrome; CML, chronic myelogenous leukemia; CP2, second chronic phase; PTCL, peripheral T-cell lymphoma; PR, partial remission; $FEV_1$, forced expiratory volume in 1 second; FL, follicular lymphoma; DLBCL, diffuse large B-cell lymphoma; MM, multiple myeloma.

evaluated by analysis of short tandem repeats in 14 patients, and complete donor chimerism was confirmed in 12 of these patients. One patient who relapsed on day 32 had exhibited 54% donor chimerism on day 30. In the remaining 3 patients who relapsed after transplantation, complete donor chimerism had been achieved by day 30. In the patient who relapsed on day 78, donor chimerism decreased from 100% on day 30 to 64% on day 60. Mixed chimerism was not confirmed in the other 2 patients before disease progression or relapse. The patients without graft failure or relapse did not have mixed chimerism during their follow-up periods.

### *3.3. Regimen-Related Toxicities and Infections*

Regimen-related toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0, and maximum toxicities are shown in Table 3. Fifteen of the 17 patients had grade III oral/pharyngeal mucositis that required morphine as an analgesic. Reversible elevation (grades III-IV) in transaminase and bilirubin levels occurred in 35% and 12% of the cases, respectively. No veno-occlusive disease was observed. Four patients developed transient grade III hyponatremia within 28 days after transplantation. Four patients developed transient pulmonary infiltration or congestive heart failure due to hypercytokinemia at engraftment, and 2 of these patients developed grade II acute GVHD after engraftment. No histologic findings of acute GVHD were seen in the other 2 patients. One patient developed reversible paroxysmal supraventricular tachycardia. One patient developed bloody diarrhea and abdominal pain even after improvement of acute GVHD of the skin, and we diagnosed intestinal thrombotic microangiopathy from the results of a gut biopsy. This patient was successfully managed by diminishing immunosuppressive treatment. Four patients who had blood cultures positive for bacterial infection (*Pseudomonas aeruginosa*, *Acinetobacter lwoffii*, *Corynebacterium* sp, and *Staphylococcus* sp) within 28 days after transplantation were successfully treated with antibiotics. Invasive aspergillosis was encountered in 2 patients (1 proven and 1 possible case). In the proven case, the patient had bronchiolitis obliterans, which was the ultimate cause of death. Of the 17 patients, CMV antigenemia was detected in 12 patients, 2 of whom had CMV colitis.

### *3.4. Graft-versus-Host Disease*

Acute GVHD of grades II to IV was diagnosed in 8 patients (48%; 95% confidence interval [CI], 36%-59%); the GVHD was grade II in 3 patients and grade IV in 5. The median time to the onset of acute GVHD was 32 days (range, 20-81 days) after transplantation (Figure 2A). Two of 4 patients who skipped methotrexate treatment on day 11 because of severe mucositis developed grade IV acute GVHD. Two of the 5 patients with grade IV acute GVHD subsequently died. One of these patients had acute GVHD after the withdrawal of CsA treatment at the time of leukemia relapse, and the other patient had received bone

**Table 2.**
Transplantation Outcomes*

| Patient No. | Time to ANC >0.5 × 10⁹/L, d | Time to Platelets >20 × 10⁹/L, d | Acute GVHD | | | | | | Chronic GVHD (Involved Organs) | Follow-up, d | Current Disease Status | Cause of Death |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Grade | Skin | Liver | Gut | mPSL, mg/kg | Response | | | | |
| 1 | 16 | 26 | IV | 3 | 4 | 4 | 2 | PG | NE | 121 | Dead | Acute GVHD |
| 2 | 35 | 30 | 0 | 0 | 0 | 0 | — | — | NE | 133 | Dead | Relapse |
| 3 | 17 | — | 0 | 0 | 0 | 0 | — | — | NE | 56 | Dead | Relapse |
| 4 | 14 | 15 | IV | 4 | 0 | 0 | 2 | CR | Ext (skin, mouth, eyes, liver, lung) | 439 | Dead | BO |
| 5 | 15 | 22 | I | 1 | 0 | 0 | — | — | Ext (skin, mouth, liver) | 286 | Dead | IP |
| 6 | 21 | 38 | II | 3 | 0 | 0 | — | — | NE | 260 | Dead | Relapse |
| 7 | 14 | 25 | I | 2 | 0 | 0 | — | — | Ext (mouth, liver) | 687+ | CR, alive | |
| 8 | 20 | 30 | II | 3 | 1 | 0 | 1 | PR | Ext (skin) | 667+ | CR, alive | |
| 9 | 22 | — | II | 3 | 0 | 0 | — | — | Ext (skin, mouth, eyes) | 336 | Dead | Organizing pneumonia |
| 10 | 18† | — | 0 | 0 | 0 | 0 | — | — | NE | 94 | Dead | Secondary graft failure |
| 11 | 16 | 23 | 0 | 0 | 0 | 0 | — | — | Ext (skin, mouth) | 564+ | CR, alive | |
| 12 | 16† | — | IV | 2 | 4 | 3 | 2 | PG | NE | 69 | Dead | Acute GVHD |
| 13 | 18 | 23 | I | 1 | 0 | 0 | 1 | CR | Ext (mouth, eyes, liver) | 525+ | CR, alive | |
| 14 | 18 | — | IV | 3 | 4 | 2 | 1 | UE | NE | 64 | Dead | Relapse |
| 15 | 14 | 16 | 0 | 0 | 0 | 0 | — | — | Ext (mouth, eyes) | 511+ | CR, alive | |
| 16 | 26 | 112 | 0 | 0 | 0 | 0 | — | — | Lim (mouth) | 463+ | CR, alive | |
| 17 | 22 | 38 | IV | 4 | 0 | 0 | 2 | CR | Ext (skin, mouth, eyes, liver, lung) | 276 | Dead | BO + aspergillosis |

*ANC indicates absolute neutrophil count; GVHD, graft-versus-host disease; mPSL, methylprednisolone; PG, progressive response; NE, not evaluable; CR, complete response; Ext, extensive disease; BO, bronchiolitis obliterans; IP, interstitial pneumonitis; PR, partial response; UE, unevaluated; Lim, limited disease.

†Secondary graft failure occurred after neutrophil recovery.

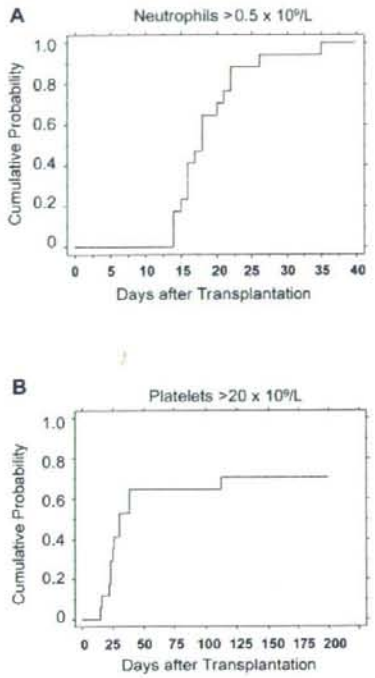


**Figure 1.** Engraftment after unrelated-donor bone marrow transplantation following reduced-intensity conditioning expressed as the cumulative probability of a neutrophil count >0.5 × $10^9$/L (A) and a platelet count >20 × $10^9$/L (B). All patients achieved neutrophil recovery, but 5 patients did not achieve platelet recovery. The median times until neutrophil and platelet recoveries were 18 days (range, 14-35 days) and 26 days (15-112 days), respectively. Late graft failure was observed in 2 patients.

marrow from a donor with allele-level mismatches at 3 HLA loci. Two patients with grade IV acute GVHD involving only the skin were successfully treated with methylprednisolone. Grade II acute GVHD involving only the skin was treated solely with CsA in 2 patients (Table 2). In 7 patients without relapse or secondary graft failure, CsA was tapered from a median of day 120 (range, day 96-169). Only 2 of the 7 patients were able to discontinue CsA (at days 203 and 288). Chronic GVHD was documented in all patients who survived beyond day 100 (1 with limited GVHD, 9 with extensive disease). There was no significant correlation between HLA disparity at the allele level and the incidence of GVHD, although it was difficult to analyze the data statistically because of the small number of patients in this study.

### *3.5. Survival and Causes of Death*

The median follow-up period was 286 days (range, 56-687 days). Overall, 11 patients died, but 6 patients are currently in remission (2 in remission and 4 not in remission at the time of transplantation). The estimated 100-day and 1-year nonrelapse mortality rates were 14% (95% CI, 12%-17%) and 46% (95% CI, 33%-57%), respectively (Figure 2B). Estimated 1-year overall survival and progression-free survival rates were both 41% (95% CI, 32%-51%; Figure 3). There were 4 deaths due to recurrent or progressive disease at a median time of 55 days (range, 32-93 days). The causes of the 7 treatment-related deaths included acute GVHD (n = 2), secondary graft failure with sepsis (n = 1), interstitial pneumonitis (n = 1), organizing pneumonia (n = 1), bronchiolitis obliterans (n = 1), and bronchiolitis obliterans with invasive aspergillosis (n = 1).

## 4. Discussion

In our previous study in an unrelated-donor BMT setting, 5 patients underwent conditioning with a combination of Flu (30 mg/m$^2$ for 6 days) or cladribine (0.11 mg/kg for 6 days), BU (4 mg/kg for 2 days), and antithymocyte globulin (2.5 mg/kg for 4 days) without TBI, but secondary graft failure in 2 of these patients alerted us to a possible higher risk of graft rejection when we used bone marrow instead of peripheral blood cells as the stem cell source. In this study, we demonstrated that the addition of 4 Gy of TBI to the widely applied combination of Flu (30 mg/m$^2$ for 6 days) and BU (4 mg/kg for 2 days) reduces the risk of graft failure and enables the rapid achievement of full donor chimerism without donor lymphocyte infusion (DLI) and that the regimen-related toxicity was acceptable. Nevertheless, a relatively high incidence of nonrelapse mortality was observed. We lost 4 patients who developed extensive chronic GVHD and subsequent pulmonary complications in the later phase, more than 6 months after transplantation. Because many patients develop extensive GVHD, we assume that the pulmonary complications were primarily due to GVHD and not the consequence of our reduced-intensity stem cell transplantation (RIST) regimen incorporating 4 Gy of TBI. However, Deeg et al reported that more pulmonary compli-

**Table 3.**
Maximum Toxicities (N = 17)*

| Grade | Cardiac, n | Mucositis, n | GI, n | Hepatic, n | CNS, n | Hyponatremia, n | Pulmonary, n | Renal, n |
|---|---|---|---|---|---|---|---|---|
| 0 | 12 | 0 | 9 | 1 | 16 | 6 | 11 | 15 |
| I | 4 | 0 | 3 | 2 | 0 | 7 | 2 | 0 |
| II | 0 | 2 | 4 | 7 | 0 | 0 | 0 | 2 |
| III | 1 | 15 | 1 | 5 | 1 | 4 | 4 | 0 |
| IV | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |

*GI indicates gastrointestinal tract; CNS, central nervous system.

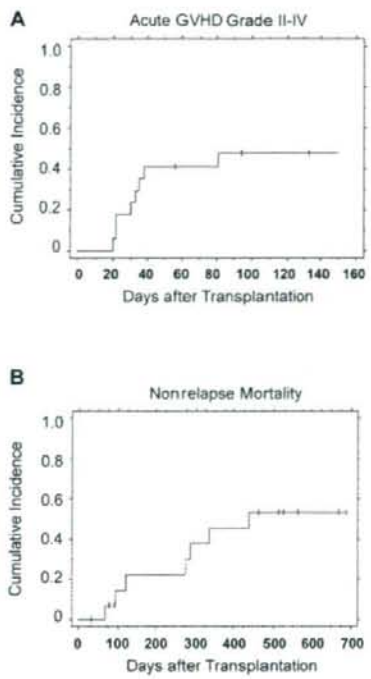


**Figure 2.** Cumulative incidence of acute GVHD (grades II-IV) (A) and nonrelapse mortality (B) after unrelated bone marrow transplantation following reduced-intensity conditioning. Acute GVHD (grades II-IV) was diagnosed in 8 patients (48%) (grade II in 3 patients and grade IV in 5) at a median of day 32 (range, day 20-81). The estimated 100-day and 1-year nonrelapse mortality rates were 14% and 46%, respectively.

cations developed in patients with aplastic anemia who received 4 to 6 Gy of TBI in combination with cyclophosphamide/antithymocyte globulin for unrelated-donor BMT than in patients who received 2 Gy TBI [20]. These investigators recommended that a 2-Gy TBI dose is sufficient to allow stable engraftment without increased toxicities, and this proposal should be evaluated in future studies. On the other hand, Maris et al described a nonmyeloablative conditioning regimen consisting of 2 Gy TBI and Flu (90 mg/m$^2$) for unrelated-donor HSCT [8]. In their study, the use of bone marrow rather than G-CSF–mobilized peripheral blood cells as the source of hematopoietic stem cells led to a lower engraftment rate (56% versus 85%), as well as lower rates of overall survival (33% versus 57%) and progression-free survival (17% versus 44%). Because bone marrow is currently the only stem cell source available from volunteer donors in Japan, we may need a more intensified regimen than the combination of 2 Gy TBI and 90 mg/m$^2$ Flu.

In this study, the rates of acute GVHD of grades II to IV and extensive chronic GVHD in patients who survived for more than 100 days were 48% and 90%, respectively. Grade IV acute GVHD was the primary cause of death in 2 patients. Moreover, the quality of life of patients who develop extensive chronic GVHD rapidly deteriorates, particularly in elderly patients. Although CsA was tapered from a median of day 120 in this series, it might be better to delay the start of CsA tapering in elderly patients, who are associated with higher GVHD rates. Studies have incorporated in vivo T-cell depletion through the addition of antithymocyte globulin or alemtuzumab in order to reduce the risk of GVHD [21-26]. In the study reported by Chakraverty et al, severe GVHD following RIST from an unrelated donor was decreased with in vivo use of alemtuzumab in the preparative regimen [23]. In their study, the rates of acute GVHD (grades II to IV) and chronic GVHD were 21% and 8%, respectively. The long half-life of alemtuzumab (15-21 days) may disturb the induction of full donor chimerism, however. If patients cannot achieve full donor chimerism, the usual option is DLI, which carries a risk of GVHD [26]. Moreover, lymphocytes for DLI are not always available for every patient, particularly in unrelated-donor transplantation settings. In this regard, we think that a regimen that routinely involves DLI after transplantation cannot be considered a universal strategy. In the present study, 2 patients who had

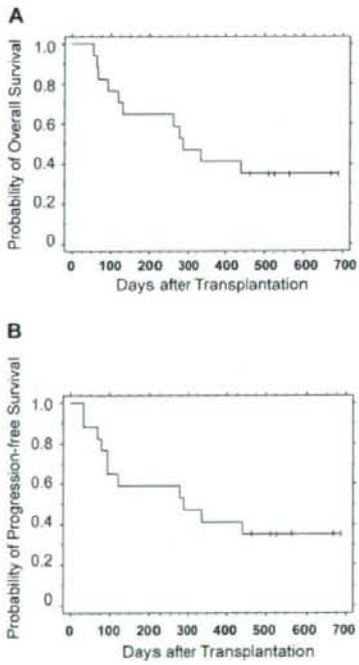


**Figure 3.** Kaplan-Meier actuarial probability of overall survival (OS) (A) and progression-free survival (PFS) (B) after unrelated-donor bone marrow transplantation following reduced-intensity conditioning. The median follow-up was 286 days (range, 56-687 days). The 1-year OS and PFS rates were both 41%. All 6 of the surviving patients (2 in remission and 4 not in remission at transplantation) remain in remission.

secondary graft failure did not receive DLI, because of grade IV acute GVHD in 1 patient and a reduced performance status in the other. Another approach to preventing severe GVHD is the use of novel immunosuppressive regimens. Several combinations of agents for GVHD prophylaxis, including CsA/mycophenolate mofetil [8,14,16] and tacrolimus/methotrexate [10,15,27], have been reported previously, and their value should be tested in prospective trials.

The induction of adequate antileukemic activity is another primary concern with a RIST procedure, particularly for patients with refractory diseases. de Lima et al reported a promising regimen that consisted of once-daily intravenous BU (130 mg/m$^2$ for 4 days) and Flu (40 mg/m$^2$ for 4 days) for patients with AML or MDS [27]. Replacement of oral BU with an intravenous preparation may result in an improved toxicity/survival profile. In our series, 4 patients achieved remission after RIST, although they were not in remission at the time of transplantation. Hence, it is likely that the antileukemic effect exerted by 4 Gy TBI in combination with Flu and BU is valuable even for the immediate control of leukemic blasts, although this possibility needs to be confirmed in further studies. The use of DLI has allowed the rescue of relapsed patients after allogeneic HSCT. In this study, however, we did not give DLI to 4 patients with progressive or relapsed diseases after transplantation because the relevance of the graft-versus-leukemia effect in rapidly proliferating diseases was not fully established and 2 of the patients had developed acute GVHD.

In conclusion, our regimen of 4 Gy TBI, Flu (180 mg/m$^2$), and BU (8 mg/kg) was effective in reducing the risk of graft failure following unrelated-donor transplantation. We confirmed, however, that a high incidence of nonrelapse mortality, primarily due to GVHD and/or pulmonary complications, still remains a major obstacle for the wider application of this procedure to elderly or medically infirm patients. Further studies to identify ways to ameliorate transplantation-related toxicities are urgently required.

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特集　血液腫瘍に対する国外大規模臨床試験の評価と国内診療へのインパクト

# 未治療骨髄腫に対する大量化学放射線療法の役割に関する米国Intergroup Trial(S9321)*

金　成元**
飛内賢正**

**Key Words** : multiple myeloma, high-dose therapy, autologous hematopoietic stem cell transplantation, allogeneic hematopoietic stem cell transplantation, S9321

## はじめに

多発性骨髄腫(multiple myeloma；MM)は，Mタンパク血症と骨病変や腎障害，造血障害，神経障害などを特徴とする形質細胞の腫瘍性疾患である．多発性骨髄腫に対する初回化学療法(寛解導入療法)の標準治療としてmelphalan(MEL)およびprednisolone(PSL)の併用(MP療法)が30年以上行われてきた．他の薬剤による併用療法も多く試されたが，MP療法を凌駕する結果は得られず，MMは生存期間中央値が3年ほどの治癒不可能な悪性腫瘍と位置づけられていた．1980年代よりMMに対するMEL大量療法の有用性が報告され，その後MEL大量療法に伴う骨髄毒性を軽減する目的で自家造血幹細胞移植を併用するようになった．自家造血幹細胞移植併用大量療法(high-dose therapy with autologous hematopoietic stem cell transplantation；HDT)はMM患者に対する治療として有望とされたが，selection biasの問題が指摘され，標準量化学療法(standard-dose therapy；SDT)との前方視的な比較研究が必要となった．1990年にフランスのIntergroupe Francophone du Myelome(IFM)[1]，1991年に同じくフランスのGroup Myeloma-Autograffe[2]，1993年に英国およびニュージーランドのMedical Research Council(MRC)[3]，1994年にスペインのPrograma de Estudio y Tratamiento de las Hemopatias Malignas(PETHEMA)[4]などにおいて，未治療症候性骨髄腫に対するHDTあるいはSDTのランダム化割付比較試験(randomized controlled trial；RCT)の患者登録が開始された．米国では，がん治療に関する3大多施設共同臨床試験グループであるSouthwest Oncology Group(SWOG)，Eastern Cooperative Oncology Group(ECOG)，およびCancer and Leukemia Group B(CALGB)のIntergroup trialとしてS9321が計画され，1993年に患者登録が開始された[5]．

## 米国Intergroup Trial S9321

### 1．方　法

S9321には，Arkansas大学，Mayoクリニック，Dana-Faberがん研究所など計11施設が参加した[5]．70歳以下，performance status(PS) 0～2(骨髄腫関連骨病変によるPS 3および4は許容)の未治療症候性骨髄腫患者を対象とした．本試験のデザインは寛解導入療法後，HDT群とSDT群にランダムに割り付け，維持療法の有無についてもランダムに割り付けるfactorial designが採用され

* Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma : final results of phase III US Intergroup Trial S9321.

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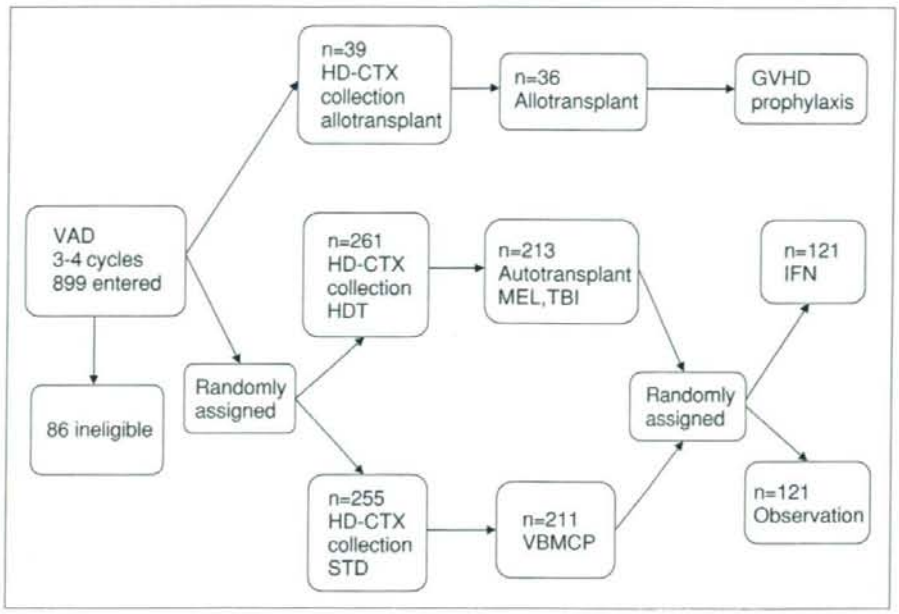


図1　治療シェーマ

ている(図1)．寛解導入療法としてはVAD療法を35日おきに繰り返し計4サイクル施行，HDTはMEL 140mg/m²を1日で投与した上で全身放射線照射(total body irradiation；TBI)12Gyを8分割4日間で施行，SDTはvincristine, carmustine, MEL, cyclophosphamide(CTX)，PSLの併用であるVBMCP療法を35日おきに繰り返し12か月間あるいは再発・進行するまで施行(12か月時点で反応が持続するならプラトー状態に達するまで継続)，維持療法としてはinterferon(IFN)α-2b 300万単位/m²を再発するまで週3回投与することとした．なお，HLA適合ドナーを有する55歳以下の患者は，TBI 12GyおよびMEL 140mg/m²を前処置とした同種造血幹細胞移植(allogeneic hematopoietic stem cell transplantation；Allo-HSCT)を受けた(ただし，36名の登録後1年治療関連死亡割合が53%となったため，Allo-HSCT群は患者登録が終了された)．HDT群，SDT群，Allo-HSCT群のいずれの群も，寛解導入療法後に大量CTX(HD-CTX)療法および末梢血幹細胞採取(peripheral blood stem cell collection；PBSCC)を試みた．Mタンパクの減少が25%未満，またはVAD療法2サイクル後にMMが進行した場合は，すみやかにHD-CTX療法およびPBSCCを行うこととした．ランダム化割付調整因子はDurie-Salmon stage(stage I-II/ IIIa/ IIIb)，診断時の血清β-2-microglobulin(B2M)値(＜6/≧6 mg/l)，VAD療法の効果(≧75%/50～74%/＜50% Mタンパク減少)であった．

## 2．結　果

899名の登録があり，うち86名が寛解導入療法開始前に不適格が判明し，248名が寛解導入療法終了時点で終了となった．患者背景においてHDT群およびSDT群に明らかな差はなかった．生存者の観察期間中央値76か月時点で，7.6%が追跡不能であった．無増悪生存期間中央値22か月，全生存期間中央値48か月，7年無増悪生存割合(progression-free survival；PFS)14%，7年全生存割合(overall survival；OS)34%であった(図2)．完全奏効(complete response；CR)，寛解(remission；R：血清Mタンパクの75%以上の減少，かつ1日尿中Mタンパク排泄量の90%以上の減少)，部分奏効(partial response；PR)，PR未満の効果(non-responder)の割合は，それぞれVAD療法後5%，46%，21%，28%，HD-CTX療法後7%，47%，20%，26%，HDT後またはSDT後11%，48%，17%，24%であった．CR割合はHDT群では17%，SDT群では15%であった．7年

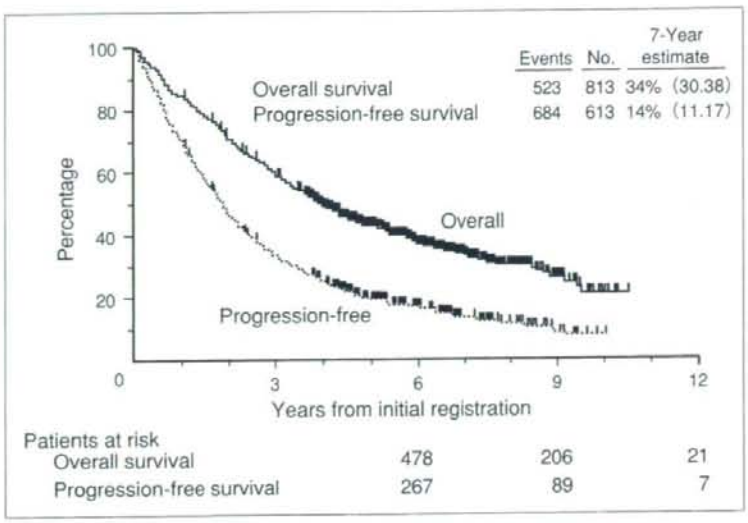


図2 全適格患者813名の全生存割合および無増悪生存割合
7年生存34%(30~38%)，7年無増悪生存14%(11~17%)．

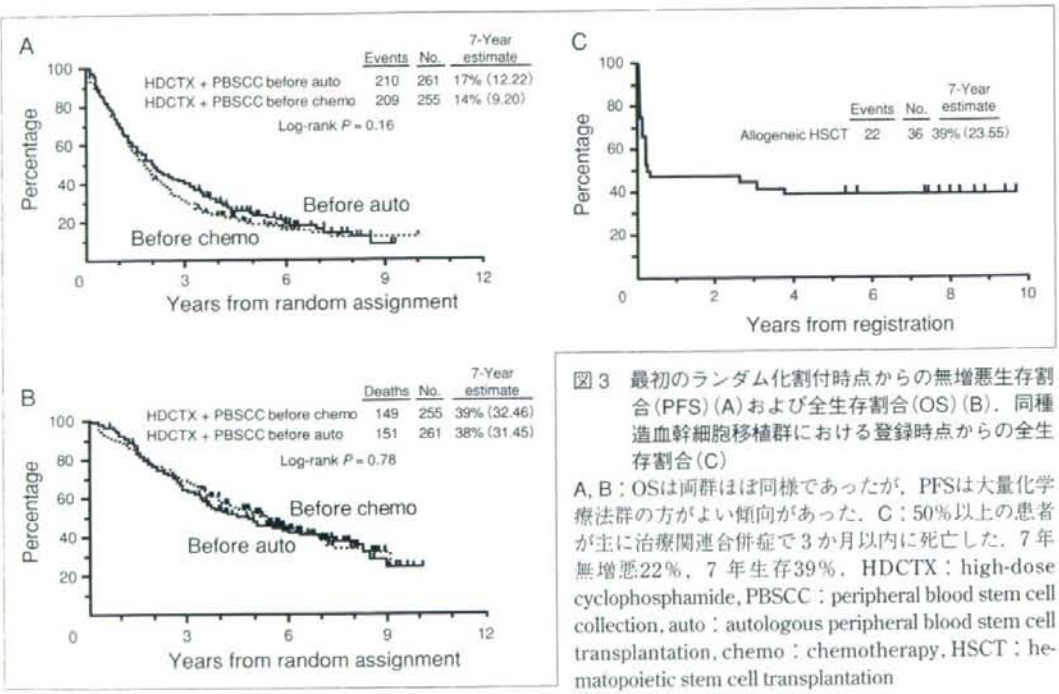


図3 最初のランダム化割付時点からの無増悪生存割合(PFS)(A)および全生存割合(OS)(B)．同種造血幹細胞移植群における登録時点からの全生存割合(C)

A, B：OSは両群ほぼ同様であったが，PFSは大量化学療法群の方がよい傾向があった．C：50%以上の患者が主に治療関連合併症で3か月以内に死亡した．7年無増悪22%，7年生存39%．HDCTX：high-dose cyclophosphamide, PBSCC：peripheral blood stem cell collection, auto：autologous peripheral blood stem cell transplantation, chemo：chemotherapy, HSCT：hematopoietic stem cell transplantation

PFSおよび7年OSはHDT群では17%および38%，SDT群では14%および39%であった(図3-A, B)．Allo-HSCT群36名におけるCR割合は17%，5年以上無増悪生存は8名，5年以上生存は14名であった(5~7年生存は40%でプラトー，図3-C)．HDTあるいはSDT後R以上の効果を示した242名に対するIFN療法群と経過観察群との比較については，PFS, OSともに統計学的有意差を認めなかった(図4)．VBMCP療法後再発をきたした157名に対する救援HDT群87名と非救援HDT群70名の比較については，生存期間中央値が30か月と23か月であった(図5)．

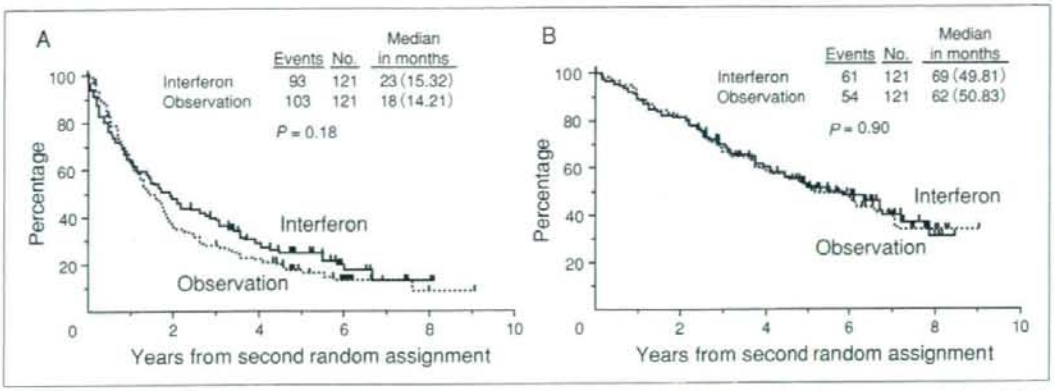


図4　経過観察あるいはinterferon維持療法のランダム化割付時点からの無増悪生存割合(A)および全生存割合(B)
解析対象はMタンパク減少割合が75%以上となった242名．両endpointともinterferonの有用性を示すことができなかった．

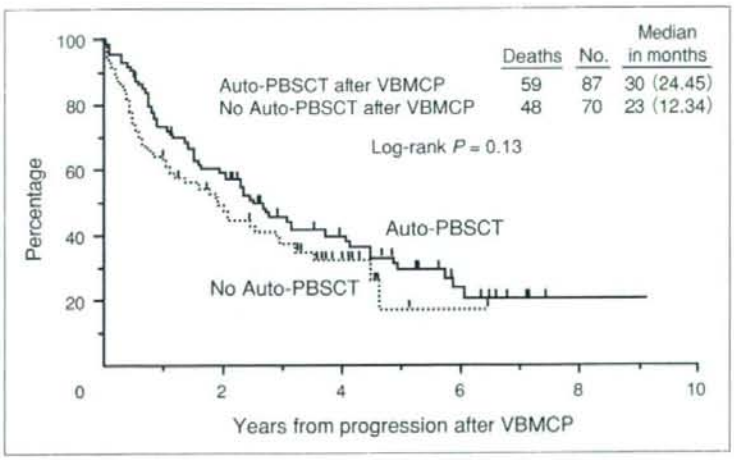


図5　VBMCP療法後増悪時点からの全生存割合
BMCP療法後増悪に対するAuto-PBSCT併用大量化学療法を受けた87名の方がsurvivalを改善させる傾向があった($P$=0.13)．Sample sizeが小さいため，Auto-PBSCT施行の有無によるsurvivalの差異を検出できなかった．Auto-PBSCT：autologous peripheral blood stem cell transplantation

PFSおよびOSに影響を及ぼす因子は，単変量解析においてB2M高値(>3.5mg/l)，LDH高値(>190U/l)，血清カルシウム(Ca)高値(≧10mg/dl)，血清クレアチニン高値(>2 mg/dl)，plasma cell labeling index(PCLI)高値(≧1 %)，血小板減少(<13万/μl)，年齢(>60歳)であり，多変量解析においてPCLI, LDH, Caであった．Fluorescence *in situ* hybridization(FISH)解析は171名(21 %)のみに施行され，13番染色体の欠失がPFSおよびOSの強力な予後不良因子であることが多変量解析によって示された．なお，治療奏効のレベルや時期はPFSやOSに影響しなかった．

VAD療法の毒性としては消化管イベント，神経症/疼痛，倦怠感が認められ，grade 3以上の血球減少が43%に認められた．VAD療法時の死亡は19名(2 %)で，死因の内訳は敗血症13名(1.6 %)，急性呼吸窮迫症候群(acute respiratory distress syndrome；ARDS)，骨髄異形成症候群，憩室炎/腹膜炎，心血管障害，脳血管障害，不明が各1名であった．HD-CTX療法時の死亡は1名で，死因は感染症であった．HDT群での死亡は8名で，死因はARDS/肺炎5名(TBI関連の毒性

と考えられている），など，SDT群での死亡は肺水腫/ARDSによる1名のみ，IFN療法時の死亡はARDSによる1名のみであった．IFN投与開始4か月の時点で毒性のため32％がIFN療法を中止した．Allo-HSCT群36名のTRMは53％と高率だったため，同群は早期中止となった．主な死因は肺炎/敗血症7名，急性graft-versus-host disease 2名であった．全患者の1年TRMは5％で，他の理由による死亡割合は1年10％，5年50％であった．

3．考　察

未治療症候性骨髄腫に対するHDTに関する大規模RCTであるS9321では，CR割合，OS，PFSのいずれもSDT群との間に統計学的に有意差が認められず，IFM90[1]やMRC VII[3]の結果と明らかに異なっていた．IFM90は200名の登録があり，CR割合22％対5％，7年OS 44％対23％と，それぞれ統計学的有意差が確認された．MRC VIIは407名の登録があり，CR割合44％対8％，7年OS 38％対26％と，それぞれ統計学的有意差が確認された．MRC VII[3]およびPATHEMA trial[4]ではHDT群のみPBSCC前にHD-CTX療法が加わっているが，S9321では両群ともHD-CTX療法が加わっている．HD-CTX療法がある分，S9321のSDT群の治療強度が高いため，両群間に統計学的有意差が確認されなかった一因になった可能性が考えられる．ちなみにIFM90では両群ともHD-CTX療法が加わっていない．また，55～65歳を対象としているGroup Myeloma-Autograffe trialではmethylprednisolone 400mg/日静注×4日間でPBSCCが施行されている[2]．

HDTのレジメンに関しては，IFM90はTBIが8 GyとS9321より少ない照射量であり，MRC VIIはPBSCを用いる場合はMEL 200mg/m$^2$単独，少数ではあるが骨髄を用いる場合はTBI（照射量不明）＋MEL 140mg/m$^2$が用いられた．TBIの強度が影響を及ぼしている可能性もある．SDTとして採用されている非交叉耐性抗がん剤による多剤併用療法については，上述の5試験で治療強度やスケジュールに大差はない．

IFM90，MRC VII，およびGroup Myeloma-Autograffe trialでは，試験登録後ただちにHDT群あるいはSDT群にランダムに割り付けたが，S9321はVAD療法による寛解導入療法後にランダムに割り付けている点が異なる．HDT群あるいはSDT群にランダムに割り付けられた516名は，寛解導入療法によってPR以上の効果を示した選ばれたMM患者と考えられる．PETHEMA trialもS9321同様，寛解導入療法に反応した患者のみを対象として両群に割り付けた．ちなみに同trialは，CR割合は30％および11％とHDT群（MEL 200mg/m$^2$）が有意に高かったが，S9321と同じくPFSおよびOSで延長効果がなかった．

2005～2006年に発表された3試験では，いずれもPFSおよびOSで延長効果がなかった[2][4][5]．生存者の追跡期間中央値を比較すると，IFM90およびMRC VIIが37か月および42か月であるのに対し，S9321，PETHEMA trial，Group Myeloma-Autograffe trialは76か月，56か月，120か月と長期であった．追跡期間の長短が影響を及ぼしている可能性もある．

MMに対するHDTが一般診療として受け入れられつつある昨今，S9321の結果は将来のHDTまたはSDTの試験デザインを考える上で重要な点を示唆している．まず，著者らはHDTレジメンにTBIを組み込むべきではないという点を指摘している．1991年のSWOG trialにおいて，hemibody irradiation（HBI）が非交叉耐性抗がん剤の併用療法よりも効果および毒性で劣ると報告されている（S8229/8230）[6]．HBIとTBIを同一視することはできないが，S9321においてもTBI関連と考えられる肺毒性で致死的となっている患者が多いことを考慮するとTBIは不要であろう．次にIFN療法の必要性について指摘している．維持療法およびup-frontとしてのIFN投与はmeta-analysisでその有用性が示唆されているが[7][8]，S9321では毒性によって投与を中止せざるを得なかった患者が多かったためか，IFNの有用性は認められなかった．MMに対して複数の有効な新規治療薬が登場していることもあり，今後の臨床試験においてIFN療法を組み込むことは少なくなっていくものと考えられる．

国際的に普及しつつあるInternational Staging System[9]に用いられる血清B2M値および血清アルブミン値については，S9321において，血清B2M値（主に腫瘍量を反映）は単変量解析で独立した

予後因子となったが，血清アルブミン値(サイトカイン，とくにIL-6の活性を反映)は予後因子とはならなかった．IFM90, MRC VII, Group Myelome-Autograffe trialにおいても血清B2M値が予後と関連することを示している．PCLI[10]および13番染色体の欠失[11][12]は他の大規模試験で予後因子としての有用性が示されている．

経口薬の併用療法であるthalidomideおよびdexamethasone(TD療法)はMMに対する初回治療として注目すべき効果を示した[13][14]．IFM94(タンデム自家移植)に関する最近の報告[15]およびTD維持療法のpreliminary data[16]を立証するために，SWOGではS0204として初回寛解導入療法およびMEL 200mg/m²を用いるタンデム自家移植後の維持療法としてのTD療法の有用性を検証中である．IFMおよびSWOGの試験結果が注目される．

S9321における55歳以下を対象としたTBI 12Gy＋MEL 140mg/m²を前処置として用いるAllo-HSCTは，2年TRMが50%以上であったが，その後の生存曲線は平坦になり，治癒に至ったと考えられる．TRMの問題が改善されれば，HDTによってもほぼ治癒不可能なMMに対する有望な治療選択になる可能性がある．TRMを減らす試みとしてreduced-intensity conditioning regimenを用いたAllo-HSCTが高齢者でも安全に施行可能であることが報じられた[17][18]．レジメンの工夫などによってAllo-HSCTの治療成績が改善される可能性がある．

## おわりに

米国Intergroup trialであるS9321について他の大規模RCTと比較しながら概説し，私見を述べた．S9321などの結果をもってHDTを否定するのではなく，新規治療薬が続々と登場することを踏まえ，HDTにおける新規治療薬の役割と投与のタイミングを検討すべきであろう．また，HDT前のmaximum cytoreductionの必要性，明確に異なる予後をもつ分子学的には別個の疾患単位と考えられるMMに関するclinical outcomeの解釈についても検証すべきである．欧米のような大規模RCTを行うのは困難かもしれないが，日本国内においてもエビデンス構築のための努力を続ける必要があると考える．

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# 4. 悪性リンパ腫に対する同種移植

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**key words** malignant lymphoma, allogeneic hematopoietic stem cell transplantation, myeloablative conditioning, nonmyeloablative conditioning, reduced-intensity conditioning, radioimmunotherapy

**動　向**

進行期あるいは再発非ホジキンリンパ腫 non-Hodgkin lymphoma (NHL) に対して根治が期待できる最も有力な治療法は依然として同種造血幹細胞移植である．中高年に多いNHLに対して，従来型の骨髄破壊的同種造血幹細胞移植を施行した場合，非再発死亡 non-relapse mortality (NRM) を高率に認めることから，近年，骨髄非破壊的あるいは移植前処置を軽減した同種造血幹細胞移植（ミニ移植）が世界的に広く施行され，短期間における有効性やNRMの減少が観察されていた．最近では，観察期間中央値30カ月以上の同種造血幹細胞移植，特にミニ移植の臨床研究結果が続々と報告されている．また，再発ホジキンリンパ腫 Hodgkin lymphoma (HL) に対する同種移植の成績も複数報告された．また，B細胞リンパ腫患者を対象としたradioimmunotherapyを移植前処置に組み込んだ同種移植の臨床試験成績が報告されるようになった．

## A. 悪性リンパ腫（全般）に対するミニ移植

イタリアから再発悪性リンパ腫に対する同胞間ミニ移植の多施設共同臨床第II相試験結果が報告された[1]．Corradiniらが用いた治療プロトコルは，移植前処置がthiotepa 10mg/kg, cyclophosphamide (Cy) 60mg/kg, fludarabine (Flud) 60mg/m$^2$であり，移植片対宿主病 graft-versus-host disease (GVHD) 予防はcyclosporine (CSP) およびmethotrexate (MTX) であった．HLA1抗原不適合移植患者3名にはday－1にalemtuzumab 7.5mg/m$^2$を追加した．症例登録期間は2001年3月から2006年9月までで，170名の登録があった．年齢中央値は51歳，診断から移植までの期間中央値は36カ月，化学療法レジメン数中央値は3，49%の患者に自家移植歴があった．登録されたindolent lymphoma 63名 (37%) の内訳は，濾胞性リンパ腫follicular lymphoma (FL) が27名，慢性リンパ性白血病/小リンパ球性リンパ腫 chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) が32名，リンパ形質細胞性リンパ腫 lymphoplasmacytic lymphoma (LPL) とMALTリンパ腫が計4名であった．その他，aggressive lymphomaが61名 (36%) (B細胞性31名，T細胞性23名，transformation 7名)，マントル細胞リンパ腫 mantle cell lymphoma (MCL)

**表1 悪性リンパ腫に対するミニ移植に関する臨床研究**

| 著者（発表年，文献） | 患者数 | 組織型/疾患タイプ | 前処置レジメン | 幹細胞ソース | 観察期間<br>中央値 |
|---|---|---|---|---|---|
| Corradini (2007) [1] | 170 | Indolent, 63<br>Aggressive, 61<br>MCL, 14<br>HL, 32 | Flud/Cy/thiotepa | PBSC, 138<br>BM, 32 | 33カ月 |
| Kusumi (2005) [2] | 112 | Indolent, 45<br>Aggressive, 58<br>Highly aggressive, 9 | Flud-based, 95<br>LD-TBI, 6<br>Others, 11 | PBSC, 86<br>BM, 20<br>CB, 6 | 24カ月 |
| Lowsky (2005) [3] | 24 | MCL, 9<br>Indolent, 7<br>Aggressive, 6<br>HL, 2 | TLI 8 Gy/ATG | PBSC | 16カ月 |
| Baron (2006) [4] | 85 | MCL, 14<br>Indolent, 12<br>Aggressive, 24<br>HL, 35 | TBI 2 Gy ± Flud | PBSC＞BM | 27カ月 |
| Khouri (2005) [13] | 78 | FL, 47<br>DLBCL, 16<br>MCL, 15 | Flud/Cy/HD-R | PBSC, 91%<br>BM, 9% | 34カ月 |
| Thomson (2005) [14] | 121 | FL, 50<br>HG-NHL, 50<br>MCL, 21 | Flud/Mel/Campath | PBSC or BM | 35カ月 |
| Khouri (2005) [6] | 47 | FL | Flud/Cy/HD-R | PBSC, 97%<br>BM, 3% | 34カ月 |
| Van Besien (2005) [15] | 205 | FL | MA, 120<br>RI, 85 | (MA) PBSC, 65%<br>(RI) PBSC, 92% | MA, 49カ月<br>RI, 36カ月 |
| Avivi (2006) [16] | 118 | DLBCL | MA, 48%<br>RI, 52% | PBSC, 70%<br>BM, 30% | |
| Peggs (2005) [7] | 49 | HL | Flud/Mel/Campath | PBSC, 37<br>BM, 12 | 32カ月 |
| Thomson (2005) [17] | 38 | HL | | | |
| Devetten (2006) [8] | 146 | HL | RI, 65%<br>non-MA, 35% | | |
| Gopal (2006) [10] | 14 | MCL, 5<br>DLBCL, 4<br>FL, 3<br>SLL, 1<br>Hairy cell leukemia, 1 | Zevalin/Flud/TBI 2 Gy | PBSC | 6カ月 |
| Khouri (2006) [11] | 7 | CLL/SLL, 3<br>FL, 2<br>DLBCL, 1<br>MCL, 1 | Zevalin/Flud/Cy/HD-R | | 16カ月 |

HG: high grade, LD: low dose, HD: high dose, MA: myeloablative, RI: reduced-intensity, RD: related donor, URD: unrelated donor

| DFS/PFS | OS | 急性GVHD II～IV度 | 慢性GVHD | TRM | 再発/増悪 |
|---|---|---|---|---|---|
| 46% @3y | 62% @3y | 35% | 52% | 14% @3y | 36% |
| 57% @3y | 59% @3y | 49% | 59% | 25% | 18% |
| 55% | 62% | 4% | 27% | 13% | 21% |
| (MCL) 57% @3y<br>(Indolent) 56% @3y<br>(Aggressive) 28% @3y<br>(HL) 8% @3y | (MCL) 64% @3y<br>(Indolent) 56% @3y<br>(Aggressive) 31% @3y<br>(HL) 35% @3y | (RD) 56%<br>(URD) 65% | (RD) 48%<br>(URD) 60% | (RD) 32% @3y<br>(URD) 28% @3y | (MCL) 35%<br>(Indolent) 0%<br>(Aggressive) 35%<br>(HL) 75% |
| | | 17% | 51% | 19% @3y | 8% |
| (FL) 68% @4y<br>(HG-NHL) 43% @4y<br>(MCL) 43% @4y | (FL) 67% @4y<br>(HG-NHL) 45% @4y<br>(MCL) 83% @4y | | | (FL) 16% @4y<br>(HG-NHL) 40% @4y<br>(MCL) 11% @4y | (FL) 24%<br>(HG-NHL) 30%<br>(MCL) 29% |
| 84% @3y | 84% @3y | | | 6% | 5% |
| | | | | | (MA) 9%<br>(RI) 21% |
| 36% @2y | 43% @2y | 32% | | 29% @2y | 35% |
| 39% @4y | 56% @4y | 16% | 14% | 16% @2y | 43% |
| | 50% @5y | | | | |
| 20% @2y | 38% @2y | 61% | 69% | 33% | |
| 50% | 64% | 50% | | 0 @day 100 | 29% |
| 71% | 71% | | | 14% | 14% |