Table 2. Serum syndecan-1 levels in myeloma patients receiving chemotherapy.

	Baseline Syndecan-1 ng/mL	*Follow-up Syndecan-1 ng/mL*
Responders (n=11)		
Median	258	106
Range	97.3-460	57.3-440
Non-responders (n=4)		
Median	327	361.7
Range	245-466	251-486

correlation was found between the level of serum β_2-microglobulin, monoclonal protein concentration or bone marrow plasma cell content. A significant decrease in median syndecan level was observed in patients responding to chemotherapy, whereas the median syndecan level did not change in non-responders. Our results indicate that there is a marked difference in the serum syndecan-1 levels in different forms of plasma cell dyscrasias. Moreover, the level of syndecan-1 is higher in patients with higher stage MM. Further evaluation of patients is needed to evaluate the role of syndecan-1 in the prognosis of MM.

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Multiple Myeloma

Oral idarubicin, dexamethasone and vincristine in the treatment of multiple myeloma: final analysis of a phase II trial

This prospective phase II study evaluated a regimen with vincristine, oral idarubicin and dexamethasone (VID) in 74 patients with multiple myeloma. A partial response was achieved in 57% (16/28) of patients with previously untreated disease and in 35% (16/46) with refractory diseases. VID chemotherapy is an effective and tolerable oral alternative in an outpatient setting for these patients.

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The combination of a continuous infusion of doxorubicin and vincristine with high-dose oral dexamethasone (VAD) has become a standard treatment for patients with multiple myeloma but the necessary central venous line causes considerable complications. Therefore, oral alternatives would be preferable. We tested such an alternative (vincristine, idarubicin and dexamethasone) in 74 patients with multiple myeloma.

For this trial, the following inclusion criteria had to be fulfilled: (i) diagnosis of multiple myeloma according to the British Columbia Cancer Agency Criteria; (ii) at least stage II disease according to the staging system of Durie and Salmon, and (iii) refractory disease (i.e. unresponsive to previous therapy) or previously untreated disease.

Vincristine was administered as an intravenous bolus injection on day 1 (2 mg). Idarubicin was given as a capsule, 10 mg/m^2 per day p.o., on days 1-4 (total dose 40 mg/m^2 per course). Dose escalation (up to 13 mg/m^2/d) and dose reduction (to 8 mg/m^2/d) was possible. Dexamethasone was given at a dose of 40 mg p.o. on days 1-4, 9-12, and 17-20. Courses were repeated starting on day 29 to reach a total of 6-8 courses. An interim report of this trial was published in 1997.[1] Response was defined by European Group for Blood and Marrow Transplantation (EBMT) criteria. Seventy-six patients were registered, but two patients were excluded after registration: one had been previously treated with idarubicin and dexamethasone and one died from pre-existing pneumonia on day 3. The remaining 74 patients (Table 1) received a total of 322 courses of VID, and a median of 4 (interquartile range 3-6). Patients with refractory disease had been heavily pretreated (Table 1). Twenty-one patients (9/46 with refractory, 12/28 with previously untreated disease) received autologous stem cell transplants; their survival data were censored at the time of transplantation. Five patients died within two months of entering the study (*early death*, two from sepsis in neutropenia in the first course) and one patient was lost to follow-up after the first course. These patients were counted as failures in the efficacy evaluation. Complete informa-

Table 1. Baseline characteristics of patients with refractory or previously untreated multiple myeloma at entry into the study.

	Previously untreated disease (n=28)	*Refractory disease (n=46)*
Male/Female	18/10	28/18
Age at entry (years)	58 (52-62)	61 (54-68)
Time from diagnosis to entry (months)	1 (1-3)	34 (15-54)
Durie-Salmon stage at entry		
IIA	4 (14%)	12 (26%)
IIB	1 (4%)	0
IIIA	14 (50%)	31 (67%)
IIIB	9 (32%)	3 (7%)
Isotype of monoclonal protein		
IgG	17 (61%)	34 (74%)
IgA	7 (25%)	9 (20%)
light chain	2 (7%)	3 (7%)
non-secretory	2 (7%)	0
N. of previous chemotherapy regimens		
0	25 (89%)	0
1	3 (11%)	26 (58%)
2	0	11 (24%)
3 or more	0	8 (18%)
N. of previous chemotherapy courses (all regimens)[a]	1, 2, 3[b]	9 (6-14)
β2-microglobulin concentration (mg/dL) at entry[a]	3.3 (2.4-9.4)	4.0 (2.5-6.4)

[a]Median and interquartile range; [b]Individual data of three patients who had received previous chemotherapy.

tion on the weekly determination of leukocyte counts was available for 211 courses. In total, WHO grade IV leukopenia ($<1.0\times10^9$/L) occurred in 13/120 (10.8%) courses in refractory patients and in 3/91 (3.3%) courses in newly diagnosed patients ($p = 0.039$). No cases of WHO grade III alopecia or WHO grade III or IV nausea and vomiting were reported. Evaluation of the dose escalation and hematologic toxicity in this study suggests that a reduced idarubicin dose of 8 mg/m^2 body surface for four days is a safer dose level for the first course, and should be recommended for all patients. The dose can then be escalated to 10 mg/m^2/d in the second course if no grade IV leukopenia occurs.

The response rates are shown in Table 2. The median duration of observation from registration into the trial for all patients was 13 months. The mobilization of peripheral stem cells – if attempted – was successful in all but 1 patient, who had received 11 courses of melphalan before 6 courses of VID. In newly diagnosed patients the Kaplan-Meier estimate of median overall survival from registration was 31 months (95%-CI: 21-41). In refractory patients the median survival was 21 months (95%-CI: 10-32). These results are comparable to those published by a group of researchers at the Glasgow Royal Infirmary who treated newly diagnosed patients with oral idarubicin and high-dose dexamethasone.[2] But are the results of our study comparable to those of trials with VAD? The combined response rate was 39% (131/332; 95%-CI: 34-45) in seven VAD trials[3-9] and 35% (95%-CI: 21-50) in our trial. The median survival in the VAD trials was between 10 and 16 months and 21 months in our trial. It must be noted, however, that these trials differ from each other and from our trial in patient selection, number of treatment courses and response criteria.

In conclusion, VID is highly effective in multiple myeloma. The use of VID instead of VAD does not appear to result in significant additional costs, it avoids the complications resulting from central venous lines and could help to meet the clear preference for oral therapy and outpatient treatment that has been documented in patients with malignant diseases[10] while maintaining comparable clinical efficacy.

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Table 2. Response rates (EBMT criteria) after chemotherapy with VID in 74 patients with multiple myeloma.

	Previously untreated disease (n=28)	*Refractory disease (n=46)*
Partial response	57% (16/28, 95%-CI:37-76%)[a]	35% (16/46, 95%-CI:21-50%)
Minimal response	25% (7/28, 95%-CI:11-45%)	33% (15/46, 95%-CI:20-48%)
Stable disease	7% (2/28, 95%-CI:1-23%)	13% (6/46, 95%-CI:5-26%)
Progressive disease	4% (1/28, 95%-CI:1-18%)	11% (5/46, 95%-CI:4-24%)
Early death/not evaluated	7% (2/28)	9% (4/46)

[a]95%-CI denotes 95%-confidence interval of the response rate.

Key words: multiple myeloma, refractory disease, idarubicin, oral application, VID.

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Stem Cell Transplantation

Allogeneic bone marrow transplantation with non-T-cell-depleted marrow from two HLA-antigen-mismatched related donors

Allogeneic BMT from 2 antigen-mismatched donors has been difficult to perform without T-cell depletion. Seven patients with advanced-stage hematologic malignancies underwent BMT with intensified graft-versus-host disease prophylaxis consisting of tacrolimus, methotrexate, and methylprednisolone. No rejection or acute GVHD ≥ grade III was observed. This preliminary result is very promising.

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In a context of unrelated bone marrow transplantation (BMT), we recently demonstrated that a combination of tacrolimus (FK506), methotrexate, and methylprednisolone almost completely suppressed acute graft-versus-host disease (GVHD).[1] A transplant of non-T-cell-depleted marrow from a 1-antigen-mismatched related donor may be feasible depending on the recipient's condition.[2] The occurrence of severe acute GVHD was reported to be associated with the degree of HLA incompatibility between the donor and recipient.[3] According to Anasetti *et al.*, the difference in the incidence of severe GVHD between 1-HLA-antigen- and 2-HLA-antigen-mismatched BMT recipients was around 10%.[4] We considered it likely that this approximately 10% increase in the incidence of severe GVHD could be overcome by intensive GVHD prophylaxis with the combination of tacrolimus, methotrexate amd methylprednisolone.

The efficacy of this combination for the prophylaxis of GVHD was examined in 7 consecutive adult patients with hematologic malignancies who were transplanted using marrow from HLA-mismatched-related donors (2-antigen-mismatches in the graft-versus-host direction) without T-cell depletion in Osaka University Hospital. All the patients lacked an available HLA-identical related or HLA-phenotypically identical unrelated donor, and urgently needed transplantation. The characteristics of the patients are shown in Table 1A. The HLA disparities between donors and recipients are shown in Table 1B. Institutional review board approval was obtained for the treatment protocol, and written informed consent was obtained from the patients and their families.

All patients underwent intensified preconditioning regimens (Table 1A), and received an unmanipulated bone marrow graft. Tacrolimus was started on the day before transplantation and given at a dose of 0.03 mg/kg/day as a continuous infusion. Methotrexate was administered at the dose of 10 mg/m^2 intravenously on day 1 and at 7 mg/m^2 on days 3, 6, and 11 after grafting. Intravenous methylprednisolone was started at a dose of 2 mg/kg/day on day 1. In the absence of acute GVHD, the doses of tacrolimus and methylprednisolone were tapered as previously described.[1] Supportive care was given as previously described.[1]

All patients achieved donor type engraftment (Table 2). Three of the 7 patients did not develop clinical acute GVHD (Table 2). Three developed grade II acute GVHD at a median of day 25 (range, day 7 to 36). The acute GVHD was manifested by skin eruption preceded by a high fever and could be controlled by increasing the dose of methylprednisolone and adding mycophenolate mofetil. Two patients developed extensive chronic GVHD. One patient died of pneumonia caused by an *Aspergillus species*. One died of respiratory failure with thrombotic microangiopathy. One died of chronic GVHD-related multi-organ failure. Cytomegalovirus (CMV) antigenemia was found in 5 out of 7 patients (71.4%), but no patient developed CMV disease. All patients except for one achieved complete remission (CR) after BMT. Only 1 of 6 patients who achieved CR after BMT had a relapse (which occurred on day 284). Two patients remain in continuous CR 700 and 672 days after transplantation with 100% performance status. They have no signs of chronic GVHD under low doses of immunosuppressive agents (tacrolimus 1-2 mg/day and prednisone <10 mg/day).