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Abstract

Melphalan, ifosfamide, prednisolone, nitrosourea [1-(4-amino-2-methyl-5-pyrimidyl)-3-(2-chloroethyl)-3-nitrosourea hydrochloride, ACNU or 1, 3-bis (2-chloroethyl)-1-nitrosourea, BCNU] and vincristine (MIP-NV) were given in combination to 48 patients with multiple myeloma. The response rate was 57% in previously untreated patients, and 39% in previously treated patients. The median survival time of previously untreated patients in stage IA + IIA was 49 months, and that of patients in stage IIIA + B was 27 months. The median survival time of stage III patients depended significantly on the duration of remission. The duration of remission and survival time of patients with relief of pain and improvement in daily activity were significantly longer than those of patients without such effects. Age, sex, blood hemoglobin concentration and bone lesion were important prognostic factors. As for the side effects, leukopenia (less than 1,000/microliter) and thrombocytopenia (less than 5 X 10(4)/microliter) occurred in 10.4% and 2.1% of the patients, respectively. It was concluded that multiple drug combination therapy with MIP-NV (MIP-NV therapy) was effective for patients with multiple myeloma at all clinical stages, because it resulted in long survival with low toxicity.

KEYWORDS: multiple myeloma, combination chemotherapy

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Combination Chemotherapy for Multiple Myeloma with Melphalan, Ifosfamide, Prednisolone, Nitrosourea and Vincristine

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Melphalan, ifosfamide, prednisolone, nitrosourea [1-(4-amino-2-methyl-5-pyrimidyl)-3-(2-chloroethyl)-3-nitrosourea hydrochloride, ACNU or 1, 3-bis (2-chloroethyl)-1-nitrosourea, BCNU] and vincristine (MIP-NV) were given in combination to 48 patients with multiple myeloma. The response rate was 57% in previously untreated patients, and 39% in previously treated patients. The median survival time of previously untreated patients in stage $I_A + II_A$ was 49 months, and that of patients in stage III_{A+B} was 27 months. The median survival time of stage III patients depended significantly on the duration of remission. The duration of remission and survival time of patients with relief of pain and improvement in daily activity were significantly longer than those of patients without such effects. Age, sex, blood hemoglobin concentration and bone lesion were important prognostic factors. As for the side effects, leukopenia ($< 1{,}000/\mu l$) and thrombocytopenia ($< 5\times10^4/\mu l$) occurred in 10.4% and 2.1% of the patients, respectively. It was concluded that multiple drug combination therapy with MIP-NV (MIP-NV therapy) was effective for patients with multiple myeloma at all clinical stages, because it resulted in long survival with low toxicity.

Key words : **multiple myeloma, combination chemotherapy**

Although chemotherapy with melphalan, with or without prednisolone, is well established for the treatment of multiple myeloma (1,2), the effectiveness of combination chemotherapy with newly developed anticancer drugs has been reported (3). In 1977, Case *et al.* (4) reported the M2 protocol, which employed vincristine, melphalan, cyclophosphamide, 1, 3-bis (2-chloroethyl)-1-nitrosourea (BCNU) and prednisolone, and which yielded a higher response rate and longer survival time than therapy with melphalan and prednisolone. We reported that combination therapy with prednisolone, sequential melphalan and ifosfamide (MIP therapy) was useful, because it induced remission in patients in the advanced stage (5), and because a favorable prognostic effect was recognized (6). However, the superior efficacy of combination chemotherapy in comparison with that of melphalan-prednisolone therapy remains controversial.

The utility of a chemotherapy program

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that combined MIP (5) with nitrosourea [BCNU or ACNU, 1-(4-amino-2-methyl-5-pyrimidinyl)-3-(2-chloroethyl)-3-nitrosourea] and vincristine (MIP-NV therapy) was evaluated in the present study.

Materials and Methods

Patients selected for this treatment program had multiple myeloma diagnosed according to the criteria of Sezaki (5), which are based on histopathological findings, bone lesion, and serum or urinary M-protein, and had resistance to previous chemotherapy. No patients were excluded because of any performance status or any type of prior chemotherapy. Patients with smoldering (7) or indolent myeloma (8) were excluded, because those patients could substantially affect the overall response rate and survival duration (9). Between 1979 and 1984, 48 patients received MIP-NV therapy. Thirty-five of these patients were previously untreated. The 13 previously treated patients had received MP, C-procabazine or ACR-VCP therapy. Twenty-nine of these patients were male, 19 were female. Their ages ranged from 41 to 80, with an average of 63.9 years. The classes of M-protein were IgG in 29 cases, IgA in 11, IgM in 1 and IgD in 3. Four patients excreted light chains only, with no other paraprotein present. The clinical stage by Durie and Salmon (10) was I_A in 5 cases, II_A in 12, III_A in 24 and III_B in 7. There were few differences in the class of M-protein, age and sex between stages I_A and II_A combined (stage I_A+II_A) and stages III_A and III_B combined (stage III_A+III_B).

MIP-NV was given, as a rule, every 35 days as follows: 8 mg/m^2 of melphalan orally on days 1-4, 1.0 g/m^2 of ifosfamide intravenously on days 1-3, 35 mg/m^2 of prednisolone orally for seven days and gradually less amounts of prednisolone until day 21, and 16 mg/m^2 of a nitrosourea derivative (ACNU or BCNU) and 1.0 mg/m^2 of vincristine intravenously on day 1. For patients with severe pancytopenia, a modified protocol (mIP-aV), in which the doses of melphalan and ACNU were reduced by half while the doses of the other drugs were unchanged, was repeated every 21 days. BCNU was used between 1979 and 1981, and ACNU was used between 1981 and 1984. Every patient received maintenance therapy with intermittent melphalan and prednisolone.

The clinical response was evaluated objectively in accordance with the criteria of Sezaki (5). The treatment was defined as "effective" when there was (*a*) a 50% or greater reduction in the product of the long and short diameters of the tumor (plasmacytoma), (*b*) recalcification or disappearance of osteolytic or punched out lesions on roentgenograms, or (*c*) a 50% or greater reduction in the M-protein concentration of the serum or urine. The treatment was defined as "modestly effective" when there was a 25-50% reduction in tumor size or M-protein concentration, a decrease from $\geqq$ 50% to less than 10% in the percentage of plasma cells in a bone marrow smear, or a reduction in the area of osteolytic or punched out lesions on roentgenograms. The treatment was defined subjectively as "effective" when there was an improvement of two or more steps in the pain-activity score (5), and as "modestly effective" when there was an improvement of one step in the score for at least 4 weeks. An excellent response (ER) was defined as when the treatment was effective according to one or more of the objective criteria and to the subjective criteria. A fair response (FR) was defined as when the treatment was effective for at least one month according to the objective criteria only. When there was neither an ER nor a FR, but the disease did not progress, the response was defined as poor. The duration of remission was defined as the time from when M-protein was reduced to 50% of the pretreatment value to when it reached 50% of its value again.

Survival time was calculated from the start of the combination chemotherapy to October, 1984 by means of the Kaplan-Meier life-table method (11), and differences in survival were evaluated by the logrank test (12). There were 19 survivors. Two patients were excluded from the survival time analysis because one patient died of myocardial infarction, and the other of gastric cancer.

Serum M-protein concentration was determined as reported elsewhere (13).

Results

Responses to treatment. The results of

Table 1 Effectiveness of combination chemotherapy for multiple myeloma[a]

Assessment parameter[b]	Number of patients[c]	Modestly effective[c]	Effective[c]	Effectiveness ratio[d] (%)	Improvement ratio[e] (%)
Size of tumor (plasmacytoma)	4(5)	0(0)	2(2)	50(40)	50(40)
Plasma cell ratio	7(2)	4(0)	—	—	57(0)
Bone lesion	30(12)	0(0)	1(0)	3(0)	3(0)
M-protein level	35(13)	6(3)	20(5)	57(39)	74(62)
Pain-activity score	28(11)	4(3)	10(4)	36(36)	50(64)

a: Forty-eight patients with multiple myeloma were treated with a combination of melphalan, ifosfamide, prednisolone, nitrosourea and vincristine.

b: Details of parameters are described under Materials and Methods.

c: Numbers of patients previously untreated (no parentheses) and previously treated (in parentheses) are shown.

d: Effectiveness ratio = % of the number of patients in whom therapy was effective in the total number of patients.

e: Improvement ratio = % of the number of patients in whom the therapy was modestly effective or effective in the total number of patients.

this study are summarized in Table 1. A 50% reduction in tumor size was achieved in 2 of 4 previously untreated patients and in 2 of 5 previously treated patients. The effectiveness ratio was 50% and 40%, respectively. As for the percentage of plasma cells in bone marrow smears, 4 of 7 previously untreated patients showed a decrease in the plasma cell ratio from more than 50% to less than 10%. In one of 30 previously untreated patients, an osteolytic lesion shown on roentgenograms disappeared (the effectiveness ratio of 3%). Twenty of the 35 previously untreated patients and 5 of the 13 previously treated patients achieved 50% or more reduction in the M-protein level (effectiveness ratio of 57% and 39%, respectively). Six of the previously untreated and 3 of the previously treated patients achieved a 25-50% reduction. Thus, the improvement ratio (sum of modestly effective and effective treatment) was 74% in previously untreated patients and 62% in previously treated patients. As judged by the pain-activity score, the treatment was effective in 10 of 28 previously untreated patients (36%) and 4 of 11 previously treated patients (36%). Fifty % of previously untreated and 64% of previously treated patients showed improvement in the score.

Of the 35 previously untreated patients, 11 patients showed an ER, and 9 patients an FR. Thus, 57% of the patients showed either an ER or FR. Among the 13 previously treated (resistant to prior therapy) patients, 2 showed an ER and 3 an FR. Thus, 39% of them exhibited a fair or excellent response.

Survival time and remission duration. The median survival time of the entire group of previously untreated patients was 43 months. The survival of patients with an ER was longer than that of patients with an FR (Fig. 1, $p < 0.05$). Fig. 2 shows the survival curves according to clinical stage. The median survival time of stage $I_A + II_A$ patients was 49 months and significantly longer than the survival time (27 months) of stage $III_A + III_B$ patients ($p < 0.05$).

Table 2 shows the correlation between the protocol of the therapy and the effectiveness and survival time according to clinical stage ($I_A + II_A$ and $III_A + III_B$). Patients in stage III_{A+B} on mIP-aV protocol showed relatively low effectiveness of treatment and short survival time, compared to patients in the same stage on the MIP-AV or MIP-BV protocol, but they were not significantly different. There was no significant difference in M-protein reduction or survival time

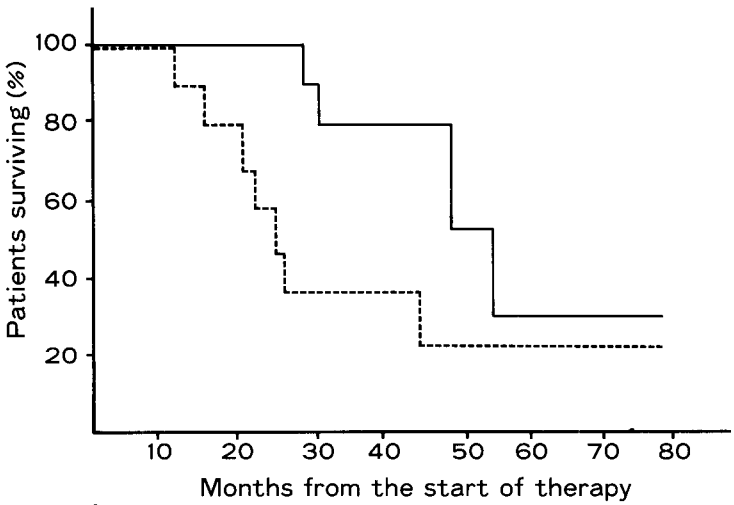

Fig. 1 Survival time of previously untreated patients as a function of responce. ——: Excellent responce with a median survival time of 50 months. ·····: Fair responce with a median survival time of 23.5 months. The survival times of both groups were significantly different ($p < 0.05$).

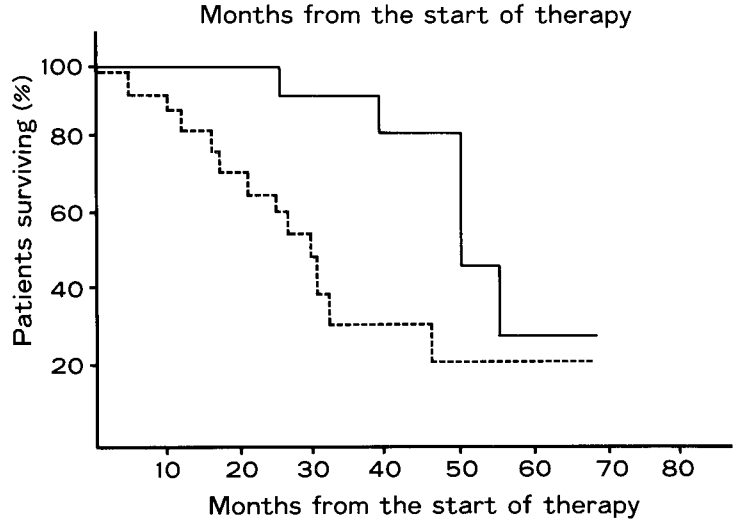

Fig. 2 Survival time of previously untreated patients as a function of clinical stage. ——: Stage I_A+II_A; 4 (I_A) and 10 (II_A) patients; median survival time, 49 months. ·····: Stage III_A+III_B; 15 (III_A) and 4 (III_B) patients; median survival time, 27 months. The survival times of both groups were significantly different ($p < 0.05$).

Table 2 Effect of chemotherapy on M-protein level and survival time of patients in different stages

Clinical stage[a]	Protocol of therapy[b]	Number of patients[c]	Number of patients who died[d]	Cases (%) with M-protein reduction of more than 50%	Median survival time (months)[e]
I_A+II_A	MIP-BV	9(8)	6	56	49
	MIP-AV	5(5)	0	40	39 (Average)
	mIP-aV	3(3)	1	33	39 (Average)
III_A+III_B	MIP-BV	7(5)	3	57	26
	MIP-AV	10(6)	4	60	31
	mIP-aV	14(8)	7	50	21

a: Clinical stages according to Durie and Salmon (10).
b: MIP-BV, combination chemotherapy with melphalan (M), ifosfamide (I), prednisolone (P), BCNU and vincristine (V); B and A, BCNU and ACNU; m, 1/2 the dose of M; a, 1/2 the dose of A. See the text for abbreviations.
c: Numbers in parentheses indicate the numbers of previously untreated patients.
d: Died before October 1984.
e: Median survival time of previously untreated patients.

Table 3 Remission duration and survival time of previously untreated patients in different stages and with different reduction rates of M-protein

Clinical stage	M-protein reduction rate (%)	Number of patients	Remission duration (R) (Average, months)	Median survival time (S) (Months)	R/S (%)
I_A+II_A	<50	7	—	40	—
	$\geqq 50$	7	25.6	49[a]	52.2
III_A	<50	5	—	28	—
	$\geqq 50$	10	25.2	26	96.9
III_B	<50	1	—	4	—
	$\geqq 50$	3	25.3	28 (Average)	90.4

a: Significantly ($p < 0.05$) longer than that of III_A ($\geqq 50\%$).

with regard to the nitrosourea derivative administered (ACNU or BCNU), in either stage I_A+II_A or stage III_A+III_B.

Table 3 shows the duration of remission and survival time of patients in different clinical stages and with different M-protein reduction rates. It was noted that, in patients in stage I_A+II_A and stage III_A, the difference in the M-protein reduction rate did not correlate to the median survival time.

Although the average duration of remission was not significantly different, the median survival time of stage I_A+II_A patients with a high M-protein reduction rate ($\geqq 50\%$) was significantly longer than that of stage III_A patients with the same reduction rate ($p < 0.05$). Therefore, the ratio of the average duration of remission to the median survival time was high in stage III_A patients (96.9%), and that in stage I_A+II_A patients was low (52.5%). This relation was almost the same in stage III_B patients as in stage III_A patients.

The average duration of remission of patients who achieved remission within 10 weeks was 32 months, and that of patients who needed more than 10 weeks to achieve remission was 10 months ($p < 0.05$).

The average duration of remission of previously treated patients was 18 months. The average survival time of previously untreated patients in stage I_A+II_A with a remission of less than 20 months was 58 months, and that of patients with a remission of more than 20 months was 44 months. Therefore, the duration of remission did not significantly correlate to the survival time. However, the median survival time of previously untreated patients in stage III_A+III_B with a remission of more than 20 months was 38 months and significantly longer than that (21 months) of patients with a remission of less than 20 months ($p < 0.005$).

The median survival time of patients in whom the therapy was effective as evaluated by both the pain-activity score and M-protein level was 45 months, which is longer than 24-months survival time of patients in whom the therapy was effective only in terms of the M-protein level ($p < 0.01$). The duration of remission of patients in whom the therapy was effective in terms of both the pain-activity score and M-protein level was 32.5 months, which is also longer than the 14.5 months-remission of patients in whom the therapy was effective only with regards to the M-protein level ($p < 0.05$). The survival time of patients without any response was 29 months. For patients who responded to therapy only in terms of pain-activity score and who had a reduction in the M-protein level of less than 25%, the average survival time was 54.5 months. Among these patient group, there were no differences in the pretreatment bone lesion scale, the pretreatment pain-activity score and the pro-

portion of stage III_{A+B} patients.

Prognostic factors. Prognostic factors generally considered to be important include the following: age, sex, M-protein (class, type, level), urinary Bence Jones protein, blood hemoglobin concentration, corrected serum calcium concentration, serum albumin, creatinine, pain-activity score and bone lesion. In the study on MIP-NV therapy, age, sex, hemoglobin concentration and bone lesion on roentgenograms proved to be important for prognosis:

Age. The median survival time of patients aged 70 or more was significantly shorter than that of patients aged less than 70 ($p < 0.025$), though no statistically significant effect of age on the prognosis was noted when the effect was evaluated according to the relative survival rate (14).

Sex. The median survival time of female patients was significantly shorter than that of male patients ($p < 0.05$). The fact that the male were 4.7 years younger on the average may explain the better prognosis of male patients. Moreover, this may be concerned with the proportion of the patients in stage $III_A + III_B$, which was 73.7% among female patients and 58.6% in male patients. When allowance was made for this factor, no statistically significant effect of sex on prognosis was found.

Blood hemoglobin concentration. The median survival time of patients with hemoglobin $\geqq 8.5$ g/dl was significantly longer than that of patients with hemoglobin < 8.5 g/dl ($p < 0.05$).

Bone lesion on roentgenograms. There was a tendency for the survival time of patients who were rated 0, 1 and 2 on the bone lesion scale to be longer than that of patients who were rated 3 on the scale.

Toxicity and complication. Leukopenia ($\leqq 1{,}000/\mu l$) occurred in 10.4% and thrombocytopenia ($\leqq 5\times10^4/\mu l$) in 2.1% of the 48 patients. Nineteen patients (39.6%) suffered from nausea and vomiting, and alopecia occurred in 14.6%. Eight patients (16.7%) suffered from infection, and one of them died as a result of sepsis. The other infections were pneumonia, cystitis, meningitis and herpes zoster. Four patients (8.3%) experienced peripheral neuropathy. Three patients (6.3%) suffered from transient liver damage. Steroid-induced glaucoma occurred in one patient. No evidence of pulmonary fibrosis or secondary malignancy was noted in any of the patients.

Discussion

It was found that the response rate of patients treated with a combination of melphalan, ifosfamide, prednisolone, nitrosourea (ACNU or BCNU) and vincristine (MIP-NV) was just as good as that of patients treated with a combination of melphalan, ifosfamide and prednisolone (MIP) (5). The median survival time of the patients in the present study, who received MIP-NV therapy, was 42 months, which was superior to that of patients who received MIP therapy. There was no correlation between M-protein level and survival time. In the M-2 protocol reported by Case *et al.* (4), the median duration of remission of previously untreated patients was more than 20 months, and median survival time of patients in stage III_A was 29 months (15). The duration of remission and median survival time of patients in stage III_A treated with MIP-NV therapy were 25.2 months and 27 months, respectively. The Myeloma Chemotherapy Study Group (16) reported the superiority of combination chemotherapy of melphalan, cyclophosphamide, vincristine, ACNU and prednisolone (MEVAP) to MEVP therapy or MP therapy with regard to survival in a randomized study, although there were no differences in response rates among these proto-

cols. Thus, nitrosourea (ACNU or BCNU) and vincristine were worth including in a combination chemotherapy. These studies confirmed the superiority of multiple drug combination therapy for patients with multiple myeloma in the advanced stage.

With respect to therapy for patients in the early stage, the median survival time of patients in stage I+II treated with M-2 protocol was 60 months, which was longer than the 20 months of patients treated with melphalan alone, and the 49 months of patients treated with MIP-NV. For early stage myeloma, it is necessary to adjust the dose of drugs to achieve a mild degree of myelosuppression, and one should expect a synergistic effect of multiple agents (17). Multiple drug combination therapy like MIP-NV therapy is superior to MP therapy in the early stage as well.

Furthermore, patients resistant to MP, CP or ACR-VCR therapy achieved an ER or FR with MIP-NV therapy. These results indicate that the effectiveness of MIP-NV therapy is superior to that of MP, MIP or other combination chemotherapies.

The survival time of patients who achieved an ER was superior to that of patients who achieved an FR ($p < 0.05$). For the therapy to affect pain and activity, a long duration of remission was necessary. The stability of the remission may lead to a long survival time. For patients in stage I_A+II_A, the survival time did not correlate to the duration of remission. On the contrary, for patients in stage III_A+III_B, the ratio of the duration of remission to the survival time was very high.

Age, sex, hemoglobin concentration and bone lesion were important prognostic factors. Hemoglobin concentration and bone lesion were incorporated into a clinical staging system by Durie and Salmon (10).

Nausea and vomiting were the most frequently observed side effects of MIP-NV therapy (39.6%). Leukopenia ($\leqq 1{,}000/\mu l$) and thrombocytopenia ($\leqq 5\times10^4/\mu l$) occurred in 10.4% and 2.1% of the patients, respectively. Chemotherapy with melphalan, ifosfamide, BCNU or vincristine has induced pulmonary fibrosis (18) and alkylating agents have been implicated as causing acute leukemia (19), but no patients developed these diseases in the present study.

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