Combination chemotherapy for multiple myeloma with melphalan, ifosfamide, prednisolone, nitrosourea and vincristine.

Hirofumi Ishii*
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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 10⁴/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 Chemoerapy 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 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 (< 1,000/µl) and thrombocytopenia (< 5×10⁴/µl) 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
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 eval-
uated 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 histo-
 pathological 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 re-
response rate and survival duration (9). Between
1979 and 1984, 48 patients received MIP-NV
therapy. Thirty-five of these patients were pre-
viously untreated. The 13 previously treated
patients had received MP, C-procarbazine 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 ex-
creted light chains only, with no other paraprotein
present. The clinical stage by Durie and Salmon
(10) was Ia in 5 cases, IIa in 12, IIIa in 24 and
IIIb in 7. There were few differences in the class
of M-protein, age and sex between stages Ia and
IIa combined (stage Ia+IIa) and stages IIIa and
IIIb combined (stage IIIa+IIIb).

MIP-NV was given, as a rule, every 35 days
follows: 8 mg/m² of melphalan orally on days
1-4, 1.0 g/m² of ifosfamide intravenously on days
1-3, 35 mg/m² of prednisolone orally for seven
days and gradually less amounts of prednisolone
until day 21, and 16 mg/m² of a nitrosourea de-
ervative (ACNU or BCNU) and 1.0 mg/m² of
vincristine intravenously on day 1. For patients
with severe pancytopenia, a modified protocol
(mMIP-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) calcification or dis-
appearance 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 ≥ 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 survi-
vors. Two patients were excluded from the sur-
vival 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

<table>
<thead>
<tr>
<th>Assessment parameter</th>
<th>Number of patients</th>
<th>Modestly effective</th>
<th>Effective</th>
<th>Effectiveness ratio (%)</th>
<th>Improvement ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of tumor (plasmacytoma)</td>
<td>4(5)</td>
<td>0(0)</td>
<td>2(2)</td>
<td>50(40)</td>
<td>50(40)</td>
</tr>
<tr>
<td>Plasma cell ratio</td>
<td>7(2)</td>
<td>4(0)</td>
<td>—</td>
<td>—</td>
<td>57(0)</td>
</tr>
<tr>
<td>Bone lesion</td>
<td>30(12)</td>
<td>0(0)</td>
<td>1(0)</td>
<td>3(0)</td>
<td>3(0)</td>
</tr>
<tr>
<td>M-protein level</td>
<td>35(13)</td>
<td>6(3)</td>
<td>20(5)</td>
<td>57(39)</td>
<td>74(62)</td>
</tr>
<tr>
<td>Pain-activity score</td>
<td>28(11)</td>
<td>4(3)</td>
<td>10(4)</td>
<td>36(36)</td>
<td>50(64)</td>
</tr>
</tbody>
</table>

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.

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 Ia + IIa patients was 49 months and significantly longer than the survival time (27 months) of stage IIIa + IIIb 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 (Ia + IIa and IIIa + IIIb). Patients in stage IIIa + IIIb 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 response. ——— Excellent response with a median survival time of 50 months. ——— Fair response 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 + II; 4 (I$\alpha$) and 10 (II$\alpha$) patients; median survival time, 49 months. ——— Stage III$\alpha$ + III$\beta$; 15 (III$\alpha$) and 4 (III$\beta$) patients; median survival time, 27 months. The survival times of both groups were significantly different ($p < 0.05$).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Effect of chemotherapy on M-protein level and survival time of patients in different stages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical stage$^a$</td>
<td>Protocol of therapy$^b$</td>
</tr>
<tr>
<td>I$\alpha$ + II$\alpha$</td>
<td>MIP-BV</td>
</tr>
<tr>
<td></td>
<td>MIP-AV</td>
</tr>
<tr>
<td>III$\alpha$ + III$\beta$</td>
<td>MIP-AV</td>
</tr>
<tr>
<td></td>
<td>mIP-aV</td>
</tr>
</tbody>
</table>

$^a$: 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

<table>
<thead>
<tr>
<th>Clinical stage</th>
<th>M-protein reduction rate (%)</th>
<th>Number of patients</th>
<th>Remission duration (R) (Average, months)</th>
<th>Median survival time (S) (Months)</th>
<th>R/S (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia+Iia</td>
<td>50% ≤ 50</td>
<td>7</td>
<td>25.6</td>
<td>40</td>
<td>52.2</td>
</tr>
<tr>
<td></td>
<td>50% ≤ 50</td>
<td>7</td>
<td>25.6</td>
<td>49a</td>
<td></td>
</tr>
<tr>
<td>IIIa</td>
<td>50% ≤ 50</td>
<td>5</td>
<td>25.2</td>
<td>28</td>
<td>96.9</td>
</tr>
<tr>
<td></td>
<td>50% ≤ 50</td>
<td>10</td>
<td>25.2</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>IIIb</td>
<td>50% ≤ 50</td>
<td>1</td>
<td>25.3</td>
<td>28</td>
<td>90.4</td>
</tr>
<tr>
<td></td>
<td>50% ≤ 50</td>
<td>3</td>
<td>25.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( a: \) Significantly \((p < 0.05)\) longer than that of IIIa \((≥ 50\%)\).

with regard to the nitrosourea derivative administered \((ACNU\) or \(BCNU\)), in either stage \(Ia+Iia\) or stage \(IIIa+IIIb\).

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 \(Ia+Iia\) and stage \(IIIa\), 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 \(Ia+Iia\) patients with a high M-protein reduction rate \((≥ 50\%)\) was significantly longer than that of stage \(IIIa\) 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 \(IIIa\) patients \((96.9\%)\), and that in stage \(Ia+Iia\) patients was low \((52.5\%)\). This relation was almost the same in stage \(IIIb\) patients as in stage \(IIIa\) 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 \(Ia+Iia\) 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 \(IIIa+IIIb\) 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 IIIA+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 IIIA+IIIA, 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 ≥ 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 (≤ 1,000/μl) occurred in 10.4% and thrombocytopenia (≤ 5×10⁴/μl) 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 IIIA was 29 months (15). The duration of remission and median survival time of patients in stage IIIA 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-
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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 (≤ 1,000/μl) and thrombocytopenia (≤ 5×10^4/μl) 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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References


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