Natural Interferon-α in Combination With Melphalan/Prednisone Versus Melphalan/Prednisone in the Treatment of Multiple Myeloma Stages II and III: A Randomized Study From the Myeloma Group of Central Sweden


Three hundred thirty-five previously untreated patients with multiple myeloma in clinical stages II and III entered a randomized trial comparing intermittent oral melphalan and prednisone (MP) therapy \( (n = 171) \) with MP in combination with the natural leukocyte-derived \( \alpha \)-interferon (MP/IFN) \( (n = 164) \). The treatment groups were comparable with regard to major prognostic factors. The response frequency was 42% in the MP group and 68% in the MP/IFN group \( (P < .0001) \). Eighty-five percent of IgA myelomas and 71% of Bence-Jones myelomas responded to MP/IFN compared with 48% and 27%, respectively, to MP treatment \( (P = .001) \). There was no difference in the overall survival between the two treatment groups. However, the survival of 72 patients with IgA or Bence-Jones myeloma randomized to receive MP/IFN was significantly longer (median 32 months) than that of 71 patients treated with MP (median 17 months) \( (P < .05) \). No statistically significant difference in response frequency (60% vs 48%) or survival was found for patients with IgG myeloma. Hematologic toxicity, WHO grades III and IV, was higher in the MP/IFN group (48%) than in the MP group (33%) \( (P < .05) \) during the induction treatment period. Fiulike syndrome was observed in 68% of patients receiving MP/IFN. The results show that MP/IFN is a well-tolerated treatment regimen, superior to MP for remission induction, and it improves significantly the overall survival for patients with IgA and Bence-Jones myelomas.

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INTERMITTENT melphalan and prednisone (MP) treatment \(^1\) is still regarded by many clinicians as one of the primary standard therapies for patients with multiple myeloma. MP induces a response rate of 40% to 50% in previously untreated patients, with a median survival of approximately 3 years. The clinical value of intensive combination chemotherapy (CCT) has been analyzed in several studies, some of which have shown an increased response rate as well as prolonged survival on CCT,\(^2,3\) whereas others have demonstrated no beneficial therapeutic effect of CCT.\(^4,7\) A recent meta-analysis comprising more than 3,800 patients demonstrated that CCT does not consistently improve the prognosis, but with the possible exception of patients with poor prognostic signs. MP might be superior in patients who have a good prognosis.\(^8\) Thus, there is a real need for other treatment approaches that may improve the outcome for patients with multiple myeloma.

Interferon-α (IFN-α) is a biologic agent that inhibits myeloma plasma cell growth in vitro in a dose-dependent manner.\(^9\) IFN-α alone \( (3 \times 10^6\) IU/d) induced a response rate of about 15% in previously untreated patients with multiple myeloma.\(^10,11\) Higher doses seemed to improve the response frequency.\(^12\) In a semisolid agar system, a synergistic effect between IFN-α and melphalan on growth inhibition of myeloma cells was noted. Prednisone had an additive effect. The inhibitory effect was dose dependent.\(^13\)

Based on these results, a randomized trial was started in April 1986 with the aim to analyze whether the addition of IFN-α to standard MP treatment could improve the therapeutic outcome of newly diagnosed patients with multiple myeloma stages II and III. This report is the final analysis.

MATERIALS AND METHODS

Patients

Six hospitals participated in the study. Three-hundred thirty-five untreated patients with multiple myeloma stages II and III\(^16\) were entered between April 1, 1986 and September 15, 1991. Patients were excluded from entry if they had stage I disease or if they had received previous chemotherapy or radiotherapy. Informed consent was obtained from each patient. Pretreatment characteristics of the patients are shown in Table 1. The two treatment groups were comparable with regard to major prognostic factors. Follow-up was performed in February 1992. One hundred and sixty patients were evaluable for response in the MP group (94%) and 157 (96%) in the MP/IFN group. All patients were evaluable for survival.

Diagnostic Criteria

The diagnosis of multiple myeloma was established when at least two of the following criteria were met: (1) a paraprotein detectable in serum or urine together with a subnormal concentration of at least one nonmonoclonal Ig class (IgG, IgM, and IgA); (2) greater than 10% plasma cells in bone marrow; and (3) osteolytic and/or osteoporotic bone lesions compatible with multiple myeloma.\(^12\)

Pretreatment evaluation included agarose electrophoresis of plasma and of 100 times concentrated urine; quantitation of plasma Igs using a nephelometer analyzer (Behring, Marburg, Germany) according to...
the manufacturer’s recommendation; quantitation of 24-hour urinary protein excretion with the Biuret technique or, alternatively, quantitation of free light Ig chains using the single radial immunodiffusion according to Mancini after pretreatment of the urine sample with polyethyleneglycol 6000 (200 g/L); roentgenographic examination of the skull, vertebral column, and pelvic bones; and examination of bone marrow (BM) specimens obtained by aspiration and/or by trephine biopsy. The percentage of plasma cells was determined by counting at least 200 cells in separate view fields of stained smears.

The initial evaluation further included erythrocyte sedimentation rate per 1 hour (ESR); hemoglobin concentration; white blood cell (WBC) count with differential; platelet and reticulocyte counts; s-albumin; s-calcium; s-creatinine; s-uric acid; and s-liver enzymes.

The clinical staging system according to Durie and Salmon was used.

Follow-Up

Every third to sixth week, the following laboratory tests were performed: ESR; hemoglobin concentration; WBC count with differential; platelet and reticulocyte counts; s-albumin; s-calcium; s-creatinine; s-uric acid; and s-liver enzymes.

Clinical response. This was defined mainly according to the criteria proposed by the Committee of the Chronic Leukemia-Myeloma Task Force. These criteria were (1) a decrease of the serum M-component concentration to less than 50% of the pretreatment value; (2) a decrease of urinary excretion of light chain protein to less than 0.2 g/24 h. In addition, patients were classified as responders only if the serum M-component and/or the urinary excretion of light chain and s-calcium concentrations were reduced to 3 mmol/L; and (4) progression of osteolytic lesions.

Criteria for progression and relapse. Progression or relapse was defined as total disappearance of the serum M-component and/or the urinary excretion of light chain protein and <5% plasma cells in the BM, hemoglobin, s-albumin, and s-calcium concentrations as for clinical response.

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The cycle length was 42 days.

When the patients fulfilled the response criteria, the IFN dose was reduced to 3 × 10^6 IU/d, subcutaneously, 3 days a week continuously and MP was continued at 6-week intervals. Treatment was continued until progression or relapse.

Statistical Analyses

Survival time was measured from the start of treatment to death or follow-up. Time to response was defined as the time from start of therapy until the date of registered response. Response duration was defined as the time from fulfilling the criteria for response until relapse, death, or follow-up. Life table analysis was applied to data. Differences in total survival and in response duration time between groups were analyzed using the log rank test taking censored data into account. Differences in distribution were tested using the X^2 analysis.

RESULTS

Response rate. Forty-two percent of the patients achieved a response in the MP group and 68% in the MP/IFN group (P < .0001) (Table 2). Median time to response was 5 months in both treatment groups. The response rate in clinical stage II patients was significantly higher in the MP/IFN group than least 25% of pretreatment or response value, respectively; (2) a 100% increase in 24-hour urinary Bence-Jones protein excretion of pretreatment or response value, respectively; (3) serum calcium ≥3 mmol/L; and (4) progression of osteolytic lesions.

**Table 1. Pretreatment Characteristics of the Patients**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>MP</th>
<th>MP/IFN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) Median</td>
<td>68</td>
<td>69</td>
</tr>
<tr>
<td>Age (yr) Range</td>
<td>(43–87)</td>
<td>(40–87)</td>
</tr>
<tr>
<td>Clinical stage II</td>
<td>73</td>
<td>69</td>
</tr>
<tr>
<td>Clinical stage III</td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td>M-component type IgG</td>
<td>93</td>
<td>87</td>
</tr>
<tr>
<td>M-component type IgA</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>M-component type Bence-Jones only</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>M-component type Non-secretory</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>M-component type IgD</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>M-component type s-creatinine</td>
<td>135</td>
<td>127</td>
</tr>
<tr>
<td>M-component type ≥170 μmol/L</td>
<td>36</td>
<td>37</td>
</tr>
<tr>
<td>M-component type &lt;170 μmol/L</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

**Table 2. Response Frequency (%) in Relation to Treatment Schedule**

<table>
<thead>
<tr>
<th>Treatment Schedule</th>
<th>MP Group (n = 160)</th>
<th>MP/IFN Group (n = 184)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Stage II</td>
<td>38 (25/69)</td>
<td>78 (50/66)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Clinical Stage III</td>
<td>46 (42/91)</td>
<td>62 (56/91)</td>
<td>.05</td>
</tr>
<tr>
<td>M-component type IgG</td>
<td>46 (40/87)</td>
<td>60 (51/85)</td>
<td>NS</td>
</tr>
<tr>
<td>M-component type IgA</td>
<td>48 (19/40)</td>
<td>85 (33/39)</td>
<td>.001</td>
</tr>
<tr>
<td>Bence-Jones only</td>
<td>27 (8/30)</td>
<td>71 (22/31)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Abbreviation: NS, not significant.

* Number of evaluable patients at analysis.
in the MP group ($P < .0001$) and in stage III the difference was almost statistically significant ($P = .05$). In patients with IgA or Bence-Jones myelomas, a significantly higher response frequency was noted in the MP/IFN group compared with the MP group ($P = .001$), whereas no significant difference was found for patients with IgG myelomas, although the numerical value was higher ($60\%$ v $46\%$).

**Complete remission rate.** Seven percent of the patients in the MP group achieved complete remission, whereas 12% in the MP/IFN group achieved complete remission.

**Total survival.** The total survival of MP/IFN-treated patients was not significantly longer than survival of patients who received MP therapy (Fig 1). The median survival was 29 months in the MP/IFN group and 27 months in the MP group. There was no significant difference in survival between the two treatment regimens when stage II and stage III patients were analyzed separately (Figs 2 and 3).

Total survival of patients with IgA and Bence-Jones myelomas is shown in Fig 4. A significantly longer survival was found for patients treated with MP/IFN compared with patients given MP therapy ($P < .05$). No significant difference in survival of IgG myelomas was noted between the two treatment regimens (Fig 5).

**Survival from response.** Survival from response of patients treated with MP/IFN was not significantly longer than the corresponding survival of patients who received MP either in the total patient material or among patients with IgA and Bence-Jones myelomas. In addition, there was no statistically significant difference in response duration time measured from onset of clinical response.

**Hematologic toxicity.** The hematologic toxicity during the induction phase is shown in Table 3. WHO grade III or IV hematologic toxicity was observed in 33% of patients on MP therapy and in 48% of patients treated with MP/IFN ($P < .05$).

During the response phase, 11% of MP/IFN-treated patients had grade IV toxicity. Thirty-three percent exhibited grade III toxicity, 35% grade II, and 15% grade I hematologic toxicity. The corresponding values for MP-treated responding...
patients were 8% of the patients exhibited grade IV toxicity, 30% grade III, 22% grade II, and 19% grade I. The differences were not statistically significant.

A similar difference in hematologic toxicity was found within the various Ig isotype subgroups as in the total material comparing the two treatment groups (data not shown).

Nonhematologic toxicity. Side effects of MP/IFN were usually moderate and tolerable. IFN-α induced transient flu-like symptoms in 68% of MP/IFN–treated patients during the induction treatment period. Gastrointestinal symptoms or reversible central nervous system (CNS) symptoms (hemiparesis, mental confusion, depression) occurred in 3% of the patients, respectively. Two patients developed allergic reactions to IFN-α. One of the patients died from nonreversible allergic shock. One patient had a myocardial infarction during the first induction cycle and another developed a severe but reversible congestive heart failure. Both patients had a history of previous but stable cardiac disease.

During the remission phase, a flu-like syndrome was observed in 18% of the patients receiving IFN maintenance therapy. Gastrointestinal symptoms occurred in two patients and CNS symptoms (reversible depression) in one patient during the response phase.

Dose reduction of melphalan. Seventy-three percent of the MP/IFN–treated patients and 64% of the MP-treated patients had no reduction of the melphalan dose during the induction treatment period. A reduction of 25% to 75% of the planned melphalan dose was done in 23% of MP/IFN–treated patients and in 34% of patients treated with MP only. Melphalan was withdrawn during the induction phase in six (4%) MP/IFN–treated patients and in three (2%) MP treated patients (Table 4).

A similar difference in reduction of the melphalan dose was noted within the Ig isotype subgroups as in the total patient population comparing the two treatment groups (data not shown).

Dose reduction of IFN-α. Fifty-six percent of MP/IFN–treated patients had no reduction of the IFN dose during the induction treatment period. A reduction of 25% to 75% of

### Table 3. Hematologic Toxicity According to WHO Grading During the Induction Phase

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Frequency (%) of WHO Grade Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>MP</td>
<td>16</td>
</tr>
<tr>
<td>MP/IFN</td>
<td>10</td>
</tr>
</tbody>
</table>

WHO grade hematologic toxicity: for leukocytes ($\times 10^9/L$): grade I, 3.0 to 3.9; grade II, 2.0 to 2.9; grade III, 1.0 to 1.9; and grade IV, less than 1.0. For platelets ($\times 10^9/L$): grade I, 75 to 99; grade II, 50 to 74; grade III, 25 to 49; and grade IV, less than 25.

### Table 4. Frequency (%) of Dose Reduction of Melphalan and IFN-α During the Induction Treatment Period

<table>
<thead>
<tr>
<th>Dose Reduction (%)</th>
<th>MP/IFN Group (n = 164)</th>
<th>MP Group (n = 171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>73</td>
<td>56</td>
</tr>
<tr>
<td>25</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>50</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>75</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>100</td>
<td>4</td>
<td>17</td>
</tr>
</tbody>
</table>

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the planned IFN-α dose was done in 27% of the patients. In 25 patients (17%), IFN-α was withdrawn during the induction phase (Tables 4 and 5).

Reduction of the IFN-α dose was similar in the different Ig isotype subgroups as in the total material.

In 25 of the responding patients, the continuous low-dose IFN-α was withdrawn during the remission phase. Nine patients had a nontolerable flulike syndrome, 6 developed leukocytopenia and/or thrombocytopenia, 5 had practical problems, 2 had nausea, 1 had depression, and myelodysplastic syndrome developed in 2 patients. Time to withdrawal during the remission phase varied between 1 and 25 months (median 8 months).

**DISCUSSION**

The prognosis of patients with multiple myeloma treated with chemotherapy has not changed markedly during the last 25 years. In younger patients, promising results have recently been presented using intensive chemotherapy regimens followed by autologous or allogeneic BM transplantation. However, as the median age of patients with multiple myeloma is about 67 years, the vast majority of patients are not candidates for such intensive treatment protocols. Therefore, other treatment regimens should be devised with the aim to improve the prognosis for patients with myeloma but with an acceptable toxicity. MP/IFN may represent such an alternative.

The results of the present study show that the addition of IFN-α to MP increased the overall response rate in previously untreated patients with myeloma approximately 50% compared to MP alone. The most striking difference in response rate between MP/IFN and MP therapy was observed for patients with IgA and Bence-Jones myelomas. Eighty-five percent of the patients with IgA myeloma and 71% of those with Bence-Jones myeloma responded to MP/IFN, whereas the corresponding frequencies for MP therapy were only 46% and 27%, respectively. There was no statistically significant difference in the IgA and Bence-Jones myeloma subgroup between the two treatment arms with regard to age, clinical stage, and renal dysfunction. IgA myeloma has also been shown in other studies to respond favorably to IFN-α therapy. Moreover, in three consecutive clinical trials, the Myeloma Group of Central Sweden (MGCS) has shown a high response rate for IgA and Bence Jones myelomas (present study). The reason for the favorable response of these myeloma subtypes is not clear. The beneficial effect might be related to the use of leukocyte-derived IFN-α. In the majority of other trials, recombinant IFN-α has been administered and mostly no difference between the various Ig isotypes was seen. It should also be noted that our patients with myeloma did not develop antibodies to leukocyte-derived IFN-α, which has been noted for IFN-α2 and IFN-α3.

Moreover, a very high response rate was noticed for patients with myeloma stage II, which has also been reported by Ludwig et al.

The high response rate in the MP/IFN group was not associated with an improved survival in the total patient population. However, in patients with IgA and Bence Jones myelomas, a statistically significant prolongation of total survival was obtained. For IgG myelomas, no difference in survival between the two treatment groups was noted. Moreover, no statistically significant difference in the response duration time and survival from response was found between the control group and study group. These findings may suggest that IFN-α might be more effective during the induction treatment than in the remission phase. Similar results have been published by Ludwig et al showing that VMCP chemotherapy plus IFN-α induced a significant prolongation of total survival but not of response duration and survival from response compared with VMCP alone. These results are further corroborated by an MRC trial showing that intensive chemotherapy compared to melphalan alone prolonged total survival but not survival from response or the response duration time.

A very high response rate as well as prolongation of survival for a regimen using MP/IFN also was reported in a small series by Montuoro et al. However, in a large patient population by Cooper et al and another by Corrado et al, no increase in the response rate and no influence on survival was observed for an MP/IFN combination therapy protocol. Kyle et al demonstrated in a nonrandomized study that 80% of previously untreated myeloma patients responded to VBMCP plus IFN-α as compared to an expected response rate of 72% for VBMCP alone. Twenty-six percent of the patients achieved a complete remission in this study. The complete remission rate for chemotherapy regimens in multiple myeloma varies from 5% to 10% for MP to 15% to 20% using CCT protocols. In intensive treatment protocols with BM rescue, the corresponding frequency is 27% to 43%. No beneficial effect of MP/IFN during the remission phase was noted in the present study, which differs from the results obtained by Mandelli et al and Westin et al, who found that a low dose of IFN-α only as maintenance therapy prolonged the remission duration time; and the Italian study also found prolonged survival from response. It should be noted, however, that in the Westin study the remission duration in the control group was only 6 months as compared with 18 months for the IFN-maintained group. Usually, the expected remission duration time for unmaintained patients is approximately 18 months. In contrast to the results of Mandelli et al and Westin et al, the German Myeloma Group found no benefit of IFN-α maintenance therapy either on

| Table 5. Reasons for Withdrawal of IFN-α During the Induction Treatment (n = 164) |
|---------------------------------|-------|
| **Cause**                       | **No. of Patients** |
| Flulike syndrome                | 7     |
| Practical problems*             | 5     |
| Leukocytopenia and/or thrombocytopenia | 4 |
| CNS symptoms                    | 3     |
| Renal dysfunction               | 2     |
| Myocardial infarction           | 1     |
| Congestive heart failure        | 1     |
| Allergic reaction               | 1     |
| Excessive diarrhea              | 1     |

*Practical problems included inability of self-administration of IFN-α, long distance to the hospital/doctor, no available district nurses.
response duration or on survival from response. The IFN-α dose in our study was similar to that of the other studies during the maintenance phase, although our patients in addition received MP treatment every sixth week. Thus, the therapeutic value of IFN-α in the remission phase is still controversial. The present study does not support a role for IFN-α during the maintenance phase.

The reasons for the varying therapeutic results obtained in the different trials combining IFN-α and chemotherapy are not obvious. Some potential causes deserve to be pointed out. In various experimental systems and in humans, a dose-response relationship for IFN-α has been noted. Also, a dose-response relationship may exist in multiple myeloma in vitro as well as in vivo. An adequate dose of IFN-α might thus be important. Comparing our study with that of Cooper et al., their patients received only 13 × 10^6 IU/m^2 of IFN-α monthly, whereas in our study the patients received 50 × 10^6 IU/m^2 monthly during the induction period. The chemotherapy constituents of these two trials are quite comparable. The importance of an adequate dose is further emphasized by the in vitro results of Klein et al., who demonstrated that low doses of IFN-α stimulated myeloma cell growth, whereas a high dose of IFN-α inhibited myeloma plasma cell proliferation.

Not only the dose of IFN-α but also the scheduling may be of importance. Based on in vitro data, IFN-α and the chemotherapeutics should be delivered concomitantly. In the large patient studies reporting a favorable effect of the combination of IFN-α and chemotherapy, the agents were administered simultaneously during the induction phase (present study). In the CALGB study, the patients also received IFN-α before administration of chemotherapeutics. As IFN-α in vitro inhibits cell cycle progression, "priming" of the tumor cells with IFN-α may make them less sensitive to subsequent administration of melphalan, which is most active against S-phase-positive cells.

Another factor of significance for the therapeutic outcome may be intermittent versus continuous IFN-α administration. Some in vitro studies have demonstrated a favorable antitumor effect of continuous IFN-α treatment when combined with chemotherapy, whereas others showed that a brief exposure to IFN-α was equally effective. Interestingly, continuous exposure of myeloma plasma cells to IFN-α in vitro downregulated the IFN receptor expression and rendered the cells resistant to further subsequent IFN-α treatment. However, when IFN-α treatment was discontinued, IFN receptors were re-expressed, resulting in restoration of the IFN-α sensitivity (K. Nilsson, personal communication, May 1992). Maybe intermittent administration of IFN-α alone or in combination with chemotherapeutic agents (present study) might add to the therapeutic success.

In conclusion, the present study shows that addition of IFN-α substantially increased the response rate of MP therapy in myeloma. It also shows that this triple-agent regimen containing IFN-α prolongs survival in IgA and Bence-Jones myelomas. It seems as if patients with IgG myeloma should not be treated with this kind of IFN-containing regimen. The antitumor activity of the regimen seems to be most pronounced during the induction phase. In the future, efforts should, therefore, be made to find an optimal induction regimen giving a qualitatively high response rate, which seems to be the best prerequisite for an improved survival.

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REFERENCES

44. Dunn CD: Effect, with time, of melphalan on hematopoietic stem cells, proliferating at different rates. J Natl Cancer Inst 51:173, 1974
Natural interferon-alpha in combination with melphalan/prednisone versus melphalan/prednisone in the treatment of multiple myeloma stages II and III: a randomized study from the Myeloma Group of Central Sweden

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