Interferon-α as maintenance therapy in patients with multiple myeloma

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Abstract

**Background:** The effect of interferon-α 2b (IFN-α) on progression free and overall survival as well as quality of life was studied in mainly elderly patients with multiple myeloma (MM), who reached a plateau phase after melphalan/prednisone induction.

**Patients and methods:** In an open phase III trial 262 patients, median age 69 (range 34-91) years, received at least 10 monthly courses of melphalan/prednisone followed by response evaluation. Plateau phase was reached by 128 patients. Next, 90 patients were randomized between IFN-α 2b and no maintenance therapy. Reasons for non-randomization were: refusal (18), concomitant disease (9), protocol violation (6), WHO performance status >2 (4), allogeneic transplantation (1).

**Results:** At a median follow-up from diagnosis of 97 (0-140) months for those patients alive, IFN-α 2b therapy was associated with improved progression free survival (median 13.5 months versus 8.4 months from randomization) though this did not translate in a better overall survival (41.0 versus 38.4 months). A third of patients discontinued IFN-α due to toxicity. No differences were observed between patient groups in quality of life.

**Conclusions:** IFN-maintenance therapy in MM prolongs progression free survival and, provided that the burden of toxicity is not too high, does not adversely affect quality of life.
Introduction

In the last years the treatment-modalities of multiple myeloma (MM) have extended enormously. High dose melphalan supported by autologous stem cell transplantation has become standard therapy for patients up to the age of 70 years. Allogeneic and especially non-myeloablative transplantations are being explored in the same age group. New anti-myeloma agents include immunomodulatory drugs (thalidomide, CC15013) and the proteosome inhibitor bortezomib\(^1\). All these treatment options have to be incorporated into studies to determine their value and place in the treatment of MM. Because stem cell transplantation is often not a viable option for patients older than 70 years with MM, melphalan and prednisone (MP) remains the standard therapy for this age-group\(^1\). Prior to the recent development in therapies mentioned interferon-\(^\alpha\) (IFN-\(\alpha\)) was investigated in the treatment of MM. Two methodologically different meta-analyses on this subject, one by using individual patient data\(^2\) and the other by using the results of published studies\(^3\) reported increases in both progression free survival and overall survival when IFN-\(\alpha\) was either used during induction or maintenance therapy for MM\(^2,3\). As IFN-\(\alpha\) might still be of value in the treatment of MM when transplantation is not an option, we investigated the data of the HOVON-16 phase III trial in which IFN-\(\alpha\) \(^2b\) maintenance therapy was compared with no maintenance therapy after plateau phase was reached with MP in mainly elderly patients with MM. With a long follow-up of 8 years for those alive, mature data were obtained. The primary endpoints were the Progression Free Survival (PFS) and Overall survival (OS); the secondary endpoint was quality of life (QoL).

Patients and methods

Patients

Between September 1991 and September 1997 31 HOVON centres entered patients with newly diagnosed MM (stage IB, IIA, II B, IIIA and IIIB) and a measurable M-protein in serum or urine. The diagnostic and staging criteria according to Salmon and Durie were used\(^4\). No previous treatment with either chemotherapy or IFN-\(\alpha\) was allowed.

Study design

All patients received induction with MP. Melphalan was given at a dose of 0.25 mg/kg for 5 days and prednisone 1.0 mg/kg for 5 days every four weeks. The minimal time of treatment with MP was 10 months even if a plateau phase was reached earlier. If after 10 months of treatment a further response was seen, treatment with MP had to
be given till a plateau phase was reached. Patients in plateau phase were candidate for randomization between IFN-α 2b or no further maintenance therapy. Patients who showed no response or who showed a relapse of their disease within 10 months after an initial response went off study.

IFN-α 2b was started at a fixed dose of 3 million units three times per week and was given till disease progression was observed. When WHO haematological grade 3 toxicity was encountered dose reduction to 50% was mandatory and in case of grade 4 toxicity IFN had to be stopped.

**Definition of disease progression and response to treatment**

Response to treatment was defined as more than 25% regression of the M-protein. A plateau phase was reached when the mean M-protein level of the last two months was at least 15% lower than the mean M-protein level of the preceding two months. Disease progression was defined as an increase of more than 25% of the mean M-protein level of the last two months compared to the mean M-protein level of the preceding two months, or progression of osteolytic lesions, hypercalcaemia and or (progression of) transfusion requirement. In case of disease progression or relapse, further therapy was given according to the discretion of the responsible physician.

**Quality of life**

For the QoL analysis the Rotterdam Symptom Checklist (RSCL) was used. The RSCL measures psychological and physical distress as experienced by cancer patients and scores for the most important three items namely 1) physical and 2) emotional capability and 3) performance of normal daily activities. This questionnaire was completed every three months by patients who were randomized after they reached plateau phase and enabled us to score the quality of life of the three items in time. All the individual scores were calculated on a scale from 0 to 100, such that a lower score implies a better functioning or well-being.

**Statistical methods**

This report contains all the data as they were available on May 2004. Response data are presented on the basis of ‘intention to treat’ (n= 262) or on the basis of those patients who actually received any therapy (n=254). All the survival analyses were performed using Kaplan-Meier plots and log-rank tests. Median survival estimates were calculated with 95% confidence intervals. In the calculation of progression free survival, patients who died without progression were censored. Response rates were compared with the Chi square tests. The mean QoL values at different time points were estimated using a linear mixed model and the QoL scores were compared by test-
ing the significance of the interaction between treatment arm and time. In this way account was taken of missing measurements due to the drop out of patients. The sample size was calculated as follows: a mean PFS from randomization of 9 months (SD 3 months) was expected. An increase of 50% of this PFS was considered as clinical useful. To show such a difference with $\alpha 0.05$ and a power of 0.90 a sample size of 40 patients per treatment arm was considered sufficient.

Results

Patients characteristics

During September 1991 - September 1997 282 patients from 31 HOVON centres were entered in the study. Not eligible were 20 patients mainly due to the absence of a good disease parameter: stage I A (6 patients), non-secretory MM (12), insufficient data (2). The median follow-up of all patients from start therapy was 30 months (range 0-140 months) and 97 months (0-140) for those alive. The median follow-up from randomization was 41 months for all patients (range 0-131 months), and 78 months for those alive (33-131). All data presented here are based upon the 262 evaluable patients (intention to treat) although eight patients actually did not receive any therapy (six died before receiving any therapy, one patient refused therapy after registration and one patient was lost to follow up shortly after the first course of therapy) and ten were not evaluable for response (mainly insufficient data available). Patient characteristics are given in Table 1.

Response rate and randomization

Response to MP was achieved in 192 (73%) patients, and 16 additional patients had some regression of their M-protein (>15% but <25%). The overall response rate was 79%. No response or progression under MP was seen in respectively 23 (9%) and 11 (4%), whereas 56 (21%) showed a response but progressed again during the first 10 months of MP therapy. Out of the 262 patients, 128 (49%) reached a plateau phase, and of those only 90 patients could be randomized. Reasons for non-randomization of these 38 patients were: refusal (18), concomitant disease (9), protocol violation (6), WHO performance status >2 (4), allogeneic transplantation (1). In total 46 patients received IFN-$\alpha$ 2b and 44 patients no maintenance therapy; both groups were similar in terms of sex, age and disease stage.
Response duration

The median PFS from randomization for patients randomized to IFN-α 2b was 13.5 months whereas those patients who did not receive any maintenance therapy showed a median PFS of 8.4 months respectively (p=0.04) (Figure 1). The PFS at three years was 25% in the IFN-α 2b group and only 4% in the control group. The median PFS from diagnosis for patients randomized was 27.3 months and 20 months respectively (p=0.01). At three years after diagnosis, the PFS was 36% in the IFN-α 2b group versus 21% in the control group.

Table 1. Patients’ characteristics.

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=262)</th>
<th>IF-alpha (n=46)</th>
<th>No IF-alpha (n=44)</th>
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<tbody>
<tr>
<td>Male/female (%)</td>
<td>54/46</td>
<td>57/43</td>
<td>48/52</td>
</tr>
<tr>
<td>Median age (range) years</td>
<td>69 (34-91)</td>
<td>68 (44-84)</td>
<td>67 (46-84)</td>
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<tr>
<td>M-protein isotype (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG/IgA/Bj/IgM/unknown</td>
<td>69/23/7/1/1</td>
<td>80/13/5/2/0</td>
<td>73/22/5/0/0</td>
</tr>
<tr>
<td>Stage (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>II A/B</td>
<td>34</td>
<td>48</td>
<td>34</td>
</tr>
<tr>
<td>III A/B</td>
<td>65</td>
<td>50</td>
<td>64</td>
</tr>
<tr>
<td>WHO performance (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>25*</td>
<td>46**</td>
<td>36**</td>
</tr>
<tr>
<td>I</td>
<td>50</td>
<td>4</td>
<td>57</td>
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<tr>
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<td>4</td>
</tr>
<tr>
<td>III</td>
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<td>2</td>
<td></td>
</tr>
<tr>
<td>IV</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Skeletal involvement (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0 lesions</td>
<td>25</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>1-5 lesions</td>
<td>35</td>
<td>41</td>
<td>37</td>
</tr>
<tr>
<td>&gt;5 lesions</td>
<td>40</td>
<td>35</td>
<td>36</td>
</tr>
</tbody>
</table>

* WHO performance at entry study
** WHO performance at randomisation
Progression free survival since randomization. The solid curve represents the patients with IFN maintenance, the thin curve those patients without maintenance therapy.

![Graph showing progression free survival](image)

**Survival**

At the moment of evaluation (August 2004), 21 patients were still alive of whom one was still in the study. In total 241 patients died of whom 169 of MM, 70 due to other causes, one patient due to MP-related toxicity, and from one patient the cause of death was unknown. The median OS of the whole patient group (n=262) was 35.1 months (95% CI 28.9-41.4 months) from the date of diagnosis (Figure 2), and 29.9 months (95% CI 23.4-36.4 months) from start of MP therapy. For patients with IgG, IgA and Bence Jones M-protein the median survival from start of therapy was 33.4, 22.9 and 20.2 months, respectively. Survival from randomization showed an advantage for patients treated with IFN-α during the first years but later survival seemed to be similar to those patients who did not receive IFN-α (Figure 2). Median survival from randomization was equal being 41.0 months and 38.4 months respectively, which demonstrates that the better PFS did not translate in a better overall survival. The median OS from diagnosis of those patients who reached plateau phase but could not be randomized was 42.8 months (95% CI 34.5-51.1 months), versus 53.5 months (95% CI 43.1-64.0) for patients treated with IFN-α and 50.2 months (95% CI 30.9-69.5) for the control group.
Toxicity

Toxicity was evaluated in the 254 patients who actually started induction therapy, of whom 17 (7%) had to end MP-therapy because of toxicity. Myelotoxicity leading to dose modification and/or treatment delay in the first 5 MP-cycles was observed in 155 patients (61%). One patient died (0.3%) due to neutropenic sepsis. Treatment with IFN-α was experienced as toxic, because 17 (37%) patients had to stop because of adverse events. Reasons why patients went off study are shown in Table 2.

Table 2. Reasons for going off study.

<table>
<thead>
<tr>
<th>Reason</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression/ no response during MP</td>
<td>68</td>
</tr>
<tr>
<td>Toxicity MP</td>
<td>17</td>
</tr>
<tr>
<td>Progression after randomization</td>
<td>60</td>
</tr>
<tr>
<td>Toxicity IFN-α 2b</td>
<td>17</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>22</td>
</tr>
<tr>
<td>Refusal to be randomized</td>
<td>18</td>
</tr>
<tr>
<td>Death due to comorbidity</td>
<td>23</td>
</tr>
<tr>
<td>Others, including 3 ineligible patients</td>
<td>36</td>
</tr>
<tr>
<td>Still in study</td>
<td>1</td>
</tr>
</tbody>
</table>
Figure 3. Estimated mean quality of life scores with 95% confidence interval. The solid curve represents the patients with IFN maintenance, the thin curve those patients without maintenance therapy. All scales are transformed into 0-100, in such a way that a lower score implies better functioning or well-being.
Quality of life

The QoL score could be calculated up to 3 years after randomization. Data are visualized in Figure 3. The score for physical well being started at 20 points (out of a range from 0-100, a score of 0 meaning no complaints at all) and although there was a slight increase in time there was no difference between the two groups (p=0.32). The score for psychological / emotional well-being started also at a score of 20 (out of a range from 0-100, a score of 0 meaning no complaints at all), showed some fluctuations in time, but there was no difference between the two groups (p=0.71). There was hardly any fluctuation in the score for daily activity. Both groups started at a score of 20 (out of a range from 0-100, a score of 0 reflecting complete normal functioning) and ended after 3 years at almost the same score without any significant difference (p=0.77).

Discussion

In this study we demonstrated that only one third of typical elderly MM-patients were candidate for IFN-α as maintenance therapy. Of these patients more than one third had to stop this therapy due to the toxicity. This means that only a minority could receive this kind of maintenance treatment for a longer period. It is thus remarkable that in the small groups studied, a significant PFS was seen in favor of those patients who received IFN-α. This did not translate in a better OS most likely because the groups were too small to detect minor differences.

IFN-α maintenance therapy in MM has yielded conflicting results as was recently addressed in a review on therapy in MM6. Two methodologically different meta-analyses on the subject of IFN-α treatment in MM have been performed investigating nearly the same data of all randomized trials on this subject6. The meta-analysis of the Myeloma Trialists’ Collaborative Group used individual patient data and observed an almost similar PFS as we did. In this meta-analysis the OS was better in patients treated with IFN-α maintenance therapy (7 months)2. However, the survival from progression was worse in the IFN-α treated patients, which may also be the explanation that the better PFS of our patients did not lead to a better OS. The meta-analysis by Fritz and Ludwig used published data instead of individual patient data and also reported a benefit for the IFN-α treatment arms3. Both meta-analyses, demonstrated a benefit of IFN-α whether it was used during induction or maintenance therapy. The greatest benefit was seen in IFN-α maintenance therapy with an OS of 72 and 3.13 months versus a prolongation of the OS of 2.43 and 22 months when IFN was used during induction therapy. For all patients (IFN-induction and IFN maintenance therapy combined) the PFS was prolonged by respectively 6 and 4.6 months2 and OS by 42 and 3.7 months3.
Interferon as maintenance therapy is associated with a wide range of possible serious side effects probably especially in elderly patients. In the Nordic Myeloma Study with patients between 55 and 81 years, more than 50% had to reduce the dose of interferon or had to stop this treatment completely\(^7\). Also in our study a substantial number of patients stopped the IFN-\(\alpha\) therapy. Ludwig \textit{et al} have shown in a cohort of 355 US myeloma patients, that 58\% of them were willing to undergo this kind of potential toxic therapy if a 6 months gain of PFS or OS could be expected\(^8\). In the Canadian study on the role of interferon maintenance therapy, patients treated with interferon experienced substantial toxicity, but also in this study patients indicated that the clinical benefits of interferon outweighed these negative effects\(^9\). On the other hand, in the Nordic QoL study in patients who received chemotherapy in combination with IFN-\(\alpha\), the reduction of the QoL was not considered by patients to justify the positive effect of IFN-\(\alpha\)\(^10\).

We conclude therefore that although improvement of the PFS and sometimes also OS can be observed when patients with MM receive IFN-\(\alpha\) as maintenance therapy after standard MP treatment, many will never be eligible for this kind of immunotherapy. However, those patients that tolerate IFN-\(\alpha\) maintenance therapy can derive benefit in terms of substantial prolongation of both PFS and OS. Evidently, one must conclude that IFN-\(\alpha\) does play a role in the treatment of these patients and should be investigated further alongside with the most recent therapeutic advances in the treatment for multiple myeloma.

**List of participating centres**

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Reference list