Dexamethasone-based regimens versus melphalan-prednisone for elderly multiple myeloma patients ineligible for high-dose therapy

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ABSTRACT

Dexamethasone alone increases life expectancy in patients with relapsed multiple myeloma (MM) ; however no large randomized study has compared dexamethasone and dexamethasone-based regimens with standard melphalan-prednisone in newly diagnosed MM patients, ineligible for high-dose therapy. In the IFM 95-01 trial, 488 patients, aged 65 to 75 years, were randomized between four regimens of treatment: melphalan-prednisone, dexamethasone alone, melphalan-dexamethasone and dexamethasone-interferon alpha. Response rates at 6 months (except for complete response) were significantly higher among patients receiving melphalan-dexamethasone and progression-free survival was significantly better among patients receiving melphalan (P < .001, for both comparisons), but there was no difference in overall survival between the 4 treatment groups. Moreover, the morbidity associated with dexamethasone-based regimens was significantly higher than with melphalan-prednisone, especially for severe pyogenic infections in the melphalan-dexamethasone arm, and hemorrhage, severe diabetes, gastrointestinal and psychiatric complications in the dexamethasone arms. Overall, these results indicated that dexamethasone should not be routinely recommended as first-line treatment in elderly patients with MM. In the context of the IFM 95-01 trial, the standard melphalan-prednisone remained the best treatment choice, when efficacy and patient comfort were both considered. These results might be useful in the context of future combinations with innovative drugs.
INTRODUCTION

In multiple myeloma (MM), melphalan and prednisone (MP) have been used since the 1960s and still remains the most widely accepted treatment option in elderly patients ineligible for high-dose therapy. Slightly different dosages and schedules have been used over the years without any demonstrated impact on survival. More complex alkylating agents combinations have often added toxicity and inconvenience without providing a survival advantage. Since the 1990s, pulse dexamethasone alone (DEX) is also frequently used, both at relapse and in untreated patients, although very limited trial results are available. In the major study of 112 untreated patients, DEX had been considered to account for most of the responses to VAD (vincristine, adriamycin, dexamethasone), with a response rate of 43% and a lower incidence of serious complications (27% for VAD versus 4% for DEX). Nevertheless, the DEX toxicity, especially neurological disturbances, psychiatric complications, secondary diabetes mellitus, gastrointestinal problems and infection susceptibility, could be a primary concern in elderly patients. Only one recent study has compared melphalan and dexamethasone (M-DEX) to MP and has concluded that MP should remain the reference for comparison of new treatments involving innovative drugs. Limited trial data are also available regarding the dexamethasone-interferon alpha (DEX-IFN) combination. In a small non randomized study of newly diagnosed patients, the addition of IFN (3 MU/m²/day) to DEX achieved results similar to those with DEX alone. In another study, DEX-IFN was given to patients who failed induction chemotherapy, and the outcome of these patients was improved with a median survival of 48 months from the start of DEX-IFN. The tolerance of DEX, M-DEX and DEX-IFN has not been fully evaluated, in the context of a large randomized trial in elderly patients.
In June 1995, the IFM group (Intergroupe Francophone du Myélome) initiated a randomized clinical trial (IFM95-01) for newly diagnosed MM patients aged 65-75 years comparing MP to dexamethasone-based regimens: M-DEX, DEX alone and DEX-IFN.

**PATIENTS AND METHODS**

**Patients**

Inclusion criteria were patients aged between 65 and 75 years and fulfilling a diagnosis of stage II or III MM according to the Durie and Salmon criteria. Durie and Salmon stage I MM patients could be enrolled, if they met one of the following criteria (defining high-risk stage I patients): presence of one lytic lesion on skeletal radiographs; bone pain with a corresponding MRI lesion; hemoglobin less than 12 g/dL for male or 11 g/dL for female, associated to the presence of >25% plasma cells in bone marrow or to M-component over 30 g/L (IgG) or 25 g/L (IgA) or 1 g/24h (light chain). Patients were previously untreated (except the minimum dose of radiotherapy to localized lesions required to relieve symptoms).

Patients were excluded if they met the criteria of primary amyloidosis or had a prior history of another neoplasm or of seizure. Patients with significant cardiac, psychiatric (including mood alterations), or hepatic dysfunction were also excluded, as well as patients who were considered to have a contra indication to high-dose steroids or who could be enrolled in IFM concomitant high-dose therapy programs. Written, informed consent was obtained from all patients before enrolment into the study.

**Study design**

This randomized, multicenter, parallel trial was carried out at 104 IFM centers in France, Belgium and Switzerland. Recruitment of patients took place between June 1995 and September
1998. Patients were randomized per center to receive MP, M-DEX, DEX, or DEX-IFN in a 1:1:1:1 ratio. Randomization was performed per center by the biostatistical center, using permutation tables of size 4 or 8 according to the expected number of enrolments within each center.

**Treatment schedules**

**MP** - The regimen consisted of 12 six-week cycles of chemotherapy. Melphalan (0.25 mg/kg) and prednisone (2 mg/kg) were given orally for 4 days. The neutrophil count must have reached $1.5 \times 10^9/L$ and the platelet count $100 \times 10^9/L$ before full dose chemotherapy was given. If the patient did not meet these criteria, treatment decision was reported one week later. At week 7 of the start of chemotherapy, full dose chemotherapy was given if the previous criteria were met, a 50% melphalan reduction was performed if the neutrophil count was between 1.0 and $1.5 \times 10^9/L$ or the platelet count between 50 and $100 \times 10^9/L$, and the decision was discussed with the trial coordinator if these levels had not been reached.

**DEX** - The treatment consisted of 12 six-week cycles of dexamethasone, 40 mg/day for 4 days beginning on days 1, 9 and 17 for the first two cycles and 40 mg/day for 4 days beginning on day 1 for the next ten cycles. The dose could be reduced by 50% (20 mg/day) in case of toxicity.

**M-DEX** - The doses of melphalan and dexamethasone and dose adjustments for side effects were the same as those presented for the MP and dexamethasone regimens.

**DEX-IFN** – IFN alfa-2b (IntronA, Schering-Plough) was administered subcutaneously at the dose of 3.0 MU three times weekly. It was started with dexamethasone and stopped on day 42 of the last dexamethasone cycle. IFN was permanently discontinued in the case of an emergence of cardiac dysfunction, or an occurrence of seizures or psychiatric complications. Protocol doses of IFN were reduced by 20 to 50% in patients who experienced significant
fatigue or other symptoms suggesting significant toxicity. The dose was subsequently reescalated if this was feasible.

**Pamidronate** – Pamidronate (AREDIA) was supplied by Ciba-Geigy and then Novartis (Basel, Switzerland). Pamidronate was administered intravenously at the dose of 90 mg within a 4 hour infusion time at day 1 of each cycle of chemotherapy (12 injections). Patients who had at diagnosis a creatinine serum level $\geq 50$ mg/L could be enrolled in the trial, but were excluded from pamidronate treatment.

**Data collection and follow-up**

At inclusion, usual clinical and biological data were collected (Table 1). Visits were planned after inclusion at 3, 6 months and every six months thereafter or up to treatment withdrawal due to either treatment toxicity, MM progression, patient consent withdrawal or death. After treatment withdrawal, patient status was regularly updated for MM progression and death. At the time of the interim and final analyses, a death-certificate based search was used to update the date of death of patients when necessary.

**End-points and sample size**

Primary end-point was overall survival (OS). Secondary end-points were progression-free survival (PFS) and survival after progression, response rates and toxicities. A strategy was a priori defined to compare survival curves between the four treatment groups: step 1. comparison between M-DEX and MP groups; step 2. comparison between DEX-IFN and DEX groups; step 3. comparison between M (melphalan) groups (MP and/or M-DEX) and DEX without M groups (DEX and/or DEX-IFN). For step 3, if a previous comparison at step 1 or 2 was clearly not significative ($P > 0.20$), the corresponding groups were collapsed before the comparison at step 3. Based on the primary end-point, the number of patients to be randomized was estimated to be
173 per group, as follows: median survival time of 24 months in the MP group, power of 80% to detect an increase in median survival time of 12 months in a two-sided test, type I error of 2%, to ensure approximately a global type I error of 5% taking into account the number of comparisons according to the pre-specified strategy, accrual time of 3 years with additional follow-up of 3 years. Assuming that 70% of enrolled patients could be analyzed, it was planned to enroll 800 patients.

Criteria of response

The achievement of any response required an improvement in bone pain and performance status, correction of hypercalcemia and no increase in size or number of lytic bone lesions. A partial response required a reduction in the size of soft tissue plasmacytomas, at least a 50% reduction in the level of the serum monoclonal protein and a reduction in 24h urinary light chain excretion by 75% or more. A complete response required the absence of the original monoclonal protein in serum and urine by immunofixation, less than 5% plasma cells in a bone marrow aspirate, and disappearance of soft tissue plasmacytomas.

Progressive disease required one or more of the following: more than 25% increase in the level of the serum monoclonal protein, which must also be an absolute increase of at least 5g/L and confirmed by at least one repeated investigation, more than 50% increase in the 24h urinary light chain excretion confirmed by at least one repeated investigation, definite increase in the size of existing bone lesions or soft tissue plasmacytomas, development of new bone lesions or soft tissue plasmacytomas, or development of hypercalcemia not attributable to any other cause. Patients not meeting the criteria of either partial or complete response or progressive disease were classified as stable disease.
**Statistical methods**

Distributions of parameters evaluated at inclusion were compared globally between treatment groups through chi-square test for categorical variables and Kruskal-Wallis rank test for continuous variables. Curves for OS, PFS and survival after progression were calculated from randomization and from progression for the latter, using the Kaplan-Meier method. Time to event (death, death or progression and death after progression) was expressed as median ± se. Relative hazards of death (RR), progression or death, death after progression, with 95% confidence interval (95%CI), were estimated through the proportional hazards model. The parameters evaluated at inclusion were analyzed for their prognostic value on overall survival from randomization, after stratification on treatment arm, through stepwise multivariate proportional hazards model, using forward selection with likelihood ratio test. In these prognostic analyses, each continuous variable was first divided into five categories at approximately the 20th, 40th, 60th and 80th percentiles. If the relative death rates (ratio of the observed number of deaths to the expected number of deaths in each category, assuming no variation of death rate across categories) in two or more adjacent categories were not substantially different, these categories were collapsed. If no clear pattern was observed, the median was used as cut-off point. Usual limits (e.g., 3 or 6 mg/L for CRP level) were also tested. As a consequence, two to three categories were used for each continuous variable. After univariate analysis, all variables with a P value less than 0.20 were proposed in several steps to multivariate analyses, first including all variables with no missing values, then proposing successively variables with an increasing number of missing values. At each step, stability of the previously derived model was checked and no further analysis was performed in case of instability. All analyses were performed on an intent-to-treat basis with SPSS software. The study was reviewed and approved by the institutional ethical committee of the University.
Hospital of Lille. Preliminary results of the trial analyzed to July 1, 1998 were reported in September, 1999. 

RESULTS

Five hundred patients were entered into the IFM 95-01 trial, between June 1995 and September 1998 with an interim analysis in July 1998. Following the interim analysis, the data safety monitoring board (DSMB) recommended to stop enrolment in the DEX arm, based on a striking disadvantage in terms of progression-free survival (\( P < 0.0001 \)) of DEX as compared to M groups (MP and M-DEX) and a trend on overall survival (\( P = 0.03 \)). Stopping enrolment in the DEX arm led to the decision to stop enrolment into the trial, since the probability to demonstrate an advantage of M-DEX or DEX-IFN as compared to MP was too low, taking into account the results available at the time of the interim analysis. Of these 500 patients, 12 were excluded from analysis because they did not fulfil the above-mentioned eligibility criteria. The clinical, radiological and biological characteristics of the 488 evaluable patients are summarized in Table 1. Of those eligible patients, 122 were allocated to receive MP, 118 to receive M-DEX, 127 to receive DEX and 121 to receive DEX-IFN. There was no difference in the distributions of pre-treatment characteristics between treatment arms. No patients were lost to follow-up.
### Table 1. Patient characteristics at enrollment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (488)</th>
<th>A (122)</th>
<th>B (118)</th>
<th>C (127)</th>
<th>D (121)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>239(49)</td>
<td>53(43)</td>
<td>63(53)</td>
<td>63(50)</td>
<td>60(50)</td>
<td>.48</td>
</tr>
<tr>
<td>Age (years)</td>
<td>70(67-72)</td>
<td>70(68-72)</td>
<td>69(68-72)</td>
<td>70(67-73)</td>
<td>69(67-72)</td>
<td>.31</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>200(41)</td>
<td>55(45)</td>
<td>45(38)</td>
<td>55(43)</td>
<td>45(37)</td>
<td>.52</td>
</tr>
<tr>
<td>Stage I</td>
<td>52(11)</td>
<td>14(11)</td>
<td>13(11)</td>
<td>16(13)</td>
<td>9(7)</td>
<td>.48</td>
</tr>
<tr>
<td>II</td>
<td>139(28)</td>
<td>43(35)</td>
<td>31(26)</td>
<td>35(28)</td>
<td>30(25)</td>
<td>.85</td>
</tr>
<tr>
<td>III</td>
<td>293(60)</td>
<td>65(53)</td>
<td>72(61)</td>
<td>75(59)</td>
<td>81(67)</td>
<td>.85</td>
</tr>
<tr>
<td>PCL**</td>
<td>4(1)</td>
<td>0</td>
<td>2(2)</td>
<td>1(1)</td>
<td>1(1)</td>
<td>.85</td>
</tr>
<tr>
<td>B substage</td>
<td>43(9)</td>
<td>13(11)</td>
<td>9(8)</td>
<td>7(6)</td>
<td>14(12)</td>
<td>.32</td>
</tr>
<tr>
<td>M-component</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>292(60)</td>
<td>71(58)</td>
<td>71(60)</td>
<td>82(65)</td>
<td>68(57)</td>
<td>.61</td>
</tr>
<tr>
<td>IgA</td>
<td>132(27)</td>
<td>36(30)</td>
<td>29(25)</td>
<td>34(27)</td>
<td>33(28)</td>
<td>.49</td>
</tr>
<tr>
<td>Bence Jones</td>
<td>44(9)</td>
<td>13(11)</td>
<td>12(10)</td>
<td>6(5)</td>
<td>13(11)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>19(4)</td>
<td>2(2)</td>
<td>6(5)</td>
<td>5(4)</td>
<td>6(5)</td>
<td></td>
</tr>
<tr>
<td>Kappa light chain¹</td>
<td>289(62)</td>
<td>78(65)</td>
<td>67(60)</td>
<td>74(61)</td>
<td>70(61)</td>
<td>.85</td>
</tr>
<tr>
<td>Bone lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>94(19)</td>
<td>26(21)</td>
<td>27(23)</td>
<td>22(17)</td>
<td>19(16)</td>
<td>.49</td>
</tr>
<tr>
<td>diffuse</td>
<td>217(45)</td>
<td>46(38)</td>
<td>53(45)</td>
<td>61(48)</td>
<td>57(47)</td>
<td>.49</td>
</tr>
<tr>
<td>others</td>
<td>176(36)</td>
<td>50(41)</td>
<td>38(32)</td>
<td>43(34)</td>
<td>45(37)</td>
<td>.49</td>
</tr>
<tr>
<td>Hemoglobin level (g/dL)²</td>
<td>10.8(9.4-12.0)</td>
<td>10.8(9.2-11.9)</td>
<td>10.7(9.5-12.0)</td>
<td>11.0(9.7-12.1)</td>
<td>10.5(9.1-11.9)</td>
<td>.17</td>
</tr>
<tr>
<td>Platelets (10⁹/L)²</td>
<td>232(178-292)</td>
<td>223(171-284)</td>
<td>245(194-310)</td>
<td>232(180-292)</td>
<td>231(181-281)</td>
<td>.27</td>
</tr>
<tr>
<td>Presence of circulating plasma cells</td>
<td>35(7)</td>
<td>6(5)</td>
<td>5(4)</td>
<td>12(10)</td>
<td>12(10)</td>
<td>.19</td>
</tr>
<tr>
<td>Serum β2 microglobulin(g/L)²</td>
<td>3.7(2.6-5.5)</td>
<td>3.7(2.6-5.9)</td>
<td>3.5(2.4-5.2)</td>
<td>3.7(2.7-5.5)</td>
<td>3.7(2.8-5.5)</td>
<td>.61</td>
</tr>
<tr>
<td>Creatinine (mg/L)²</td>
<td>10.7(9.0-13.0)</td>
<td>10.4(8.9-12.7)</td>
<td>10.4(9.0-13.0)</td>
<td>10.2(8.6-13.0)</td>
<td>11.4(9.4-14.0)</td>
<td>.11</td>
</tr>
<tr>
<td>Serum calcium (mg/L)²</td>
<td>95(90-101)</td>
<td>95(90-100)</td>
<td>95(90-100)</td>
<td>95(90-102)</td>
<td>96(91-105)</td>
<td>.37</td>
</tr>
<tr>
<td>Serum albumin (g/L)²</td>
<td>38.0(34.0-42.0)</td>
<td>38.0(34.3-42.0)</td>
<td>39.0(35.0-42.0)</td>
<td>37.0(32.3-42.8)</td>
<td>37.0(34.5-42.0)</td>
<td>.43</td>
</tr>
<tr>
<td>LDH (UI/L)³</td>
<td>295(219-399)</td>
<td>291(221-426)</td>
<td>339(214-410)</td>
<td>301(225-387)</td>
<td>285(219-365)</td>
<td>.68</td>
</tr>
<tr>
<td>CRP (mg/L)⁴</td>
<td>5(3-13)</td>
<td>5(3-15)</td>
<td>5(3-15)</td>
<td>5(3-13)</td>
<td>5(3-12)</td>
<td>.99</td>
</tr>
</tbody>
</table>

* Chi square and Kruskal-Wallis tests for qualitative and quantitative characteristics, respectively
** PCL= plasma cell leukemia
¹ n=468; ² n=447; ³ n=435; ⁴ n=449

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**Effect of treatment on response, progression-free survival and survival**

Complete responses were rare in all treatment arms, less than 2% at 6 months, with no difference between the four treatment groups. The achievement of at least a partial response was more frequent with M-DEX (70 % at 6 months) as compared to other treatment groups (about 41% at 6 months), and this difference was statistically significant (P < 0.001) (Table 2).
Table 2. Response to treatment at 6 months in the IFM 95-01 trial (expressed in % of patients)

<table>
<thead>
<tr>
<th>Category of response</th>
<th>MP (n=109)</th>
<th>M-DEX (n=110)</th>
<th>DEX (n=109)</th>
<th>DEX-IFN (n=101)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least partial</td>
<td>41</td>
<td>70</td>
<td>40</td>
<td>42</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Complete</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0.59</td>
</tr>
</tbody>
</table>

After a median follow-up time of 82.8 ± 1.6 months, the median survival time for the whole series was 35.0 ± 1.6 months (415 deaths) and the median progression-free survival time was 18.3 ± 0.8 months (473 progressions or deaths without progression). The median progression-free survival time was significantly longer in M groups, 22.4 ± 1.2 months, than in DEX without M groups, 12.6 ± 1.3 months (RR 1.55, 95% CI 1.30-1.86, P < 0.001), even if this difference did not convert into a survival advantage for patients receiving melphalan (Figure 1A,B). Indeed, as described on Figure 1A, there was no significant difference in survival between the four treatment groups; between MP and M-DEX (RR=1.17, P = 0.27), between DEX and DEX-IFN groups (RR=1.05, P= 0.75), and between DEX without M groups (DEX and DEX-IFN) and M groups (MP and M-DEX), with a survival time (median ± se) of 37.9 ± 2.3 and 32.8 ± 2.1 months, respectively (RR=1.16, 95% CI 0.95-1.40, P=0.14). This result was concordant with a longer survival after the first progression for patients receiving DEX without M, 19.9 ± 2.0 months, as compared to those receiving M, 14.2 ± 1.8 months (Figure 1C) (RR 1.30; 95%CI 1.04-1.62; P=0.02). Second line treatments are summarized in Table 3. The vast majority of patients enrolled in DEX without M groups received alkylating agent-based regimens at time of first relapse. In the late period of the study (after January 1999), some relapsed patients received thalidomide, which was equally distributed arms (17 patients in MP, M-DEX, and DEX ; 10 patients in DEX-IFN).
Table 3. Second line treatment in the context of the IFM 95-01 trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>O/N</th>
<th>Survival time median ± se (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP (n=122)</td>
<td>106/122</td>
<td>34.0 ± 3.6</td>
</tr>
<tr>
<td>M + DEX (n=118)</td>
<td>97/118</td>
<td>39.6 ± 3.1</td>
</tr>
<tr>
<td>DEX (n=127)</td>
<td>110/127</td>
<td>33.4 ± 2.0</td>
</tr>
<tr>
<td>DEX + IFN (n=121)</td>
<td>102/121</td>
<td>32.0 ± 5.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>O/N</th>
<th>Progression-free survival time median ± se (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP (n=122)</td>
<td>120/122</td>
<td>21.1 ± 1.7</td>
</tr>
<tr>
<td>M + DEX (n=118)</td>
<td>112/118</td>
<td>22.9 ± 2.0</td>
</tr>
<tr>
<td>DEX (n=127)</td>
<td>123/127</td>
<td>12.2 ± 1.0</td>
</tr>
<tr>
<td>DEX + IFN (n=121)</td>
<td>118/121</td>
<td>15.2 ± 2.7</td>
</tr>
</tbody>
</table>

Figure 1. A Survival from entry into the trial according to treatment; B progression-free survival from entry into the trial according to treatment; C survival from time of the first progression according to treatment. O/N = number of events (deaths, deaths or progressions, deaths after progression)/total number of patients.
**Survival prognostic factors**

Independent factors having an adverse impact on survival were a high serum calcium level ($\geq 110 \text{ mg/L, } P < 0.001$), an elevated serum $\beta$2microglobulin level with 2 cut-off ($> 2.5$ and $> 4.0 \text{ mg/L, } P < 0.001$), a poor OMS index at inclusion ($> 1, P < 0.001$), a low platelet count ($\leq 150 \times 10^9/\text{L, } P = 0.002$), a high white blood cell count ($> 7.5 \times 10^9/\text{L, } P = 0.02$), and a low hemoglobin level ($\leq 9\text{g/dL, } P = 0.02$). When adjusting on these prognostic factors, the results obtained for the overall survival comparisons between treatment groups were confirmed, with no difference between MP and M-DEX (RR=1.01, $P=0.93$), DEX and DEX-IFN (RR=1.10, $P=0.51$), and DEX without M and M groups (RR=1.12, 95% CI = 0.92-1.38, $P=0.26$).

**Causes of death**

Thirty five deaths occurred in the first 3 months (early deaths) representing $7.2 \pm 1.2 \%$ (mean $\pm$ se of Kaplan-Meier estimate in the whole population). Early deaths were significantly more frequent ($P = 0.004$) in the DEX without M groups ($10.5 \pm 2.0 \%$) than in the M groups ($3.8 \pm 1.2 \%$). Thirteen out of these 35 early deaths (37 \%) were related to myeloma progression. Causes of death in the first 3 months of treatment were analyzed according to treatment allocation (Table 4). Deaths related to MM progression were more frequent in patients receiving DEX without M than in patients receiving M (5\% versus 0.5\%, $P=0.003$). Except for more cancers, including myelodysplastic syndrome/secondary leukemia in M groups (4 \%) than in DEX without M groups (0.5\%) ($P = 0.02$), no differences were found between treatment groups with respect to causes of death after 3 months.
Table 4. Causes of death in the first 3 months during the IFM 95-01 trial analyzed by treatment allocation

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>Total No. (n=488)</th>
<th>MP (n=122)</th>
<th>M-DEX (n=118)</th>
<th>DEX (n=127)</th>
<th>DEX –IFN (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloma progression</td>
<td>341</td>
<td>1</td>
<td>-</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Died unexpected at home</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Cause not known</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyogenic infection when tumour load not immediately life threatening</td>
<td>28</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Neurological</td>
<td>5</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Perforated diverticulum</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>4</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MDS/secondary leukemia</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other cancer**</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other cause**</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1**</td>
</tr>
</tbody>
</table>

*Deaths in first month were as follows; MP = 1 patient, M-DEX = 1 patient, DEX = 5 patients, DEX-IFN = 6 patients; **Suicide

Toxicity

No significant differences in severe hematological toxicity were noted between MP and M-DEX; 18 patients (15%) and 20 patients (17%) displayed grade 3-4 hematological toxicity in MP and M-DEX, respectively. No myelosuppression was observed with DEX alone. In the DEX-IFN arm, IFN had to be stopped or reduced (25-50% dose reduction) due to myelosuppression in 1 and 12 patients, respectively. In the DEX-IFN arm, 28 patients (23%) had to stop IFN because of IFN-related (or at least partially related) toxicity; arythmia in 2
patients, intolerance in 13 patients (with refusal in 2 patients), refusal in 2 other patients, depression in 3 patients, severe confusion with hallucinations in 4 patients (which could also be DEX-related), seizure in 1 patient, hematotoxicity in 1 patient, hepatotoxicity in 1 patient and miscellaneous in 1 patient. IFN was stopped between month 1 and month 12, at a median time of 3 months. In addition, 30 patients (24%) had to reduce by 20 to 50% at a median time of 3 months the IFN dosage in relation to toxicity.

Severe non hematological toxicities are presented according to treatment allocation in Table 5. Severe pyogenic infections were more frequent in the M-DEX arm compared to other arms; 19% vs 10%, 11% and 9% among patients on MP, DEX and DEX-IFN, respectively (P = 0.01), and this was mainly due to a higher incidence of pneumopathy. When haemorrhage, severe diabetes, perforated diverticulum and psychiatric complications were considered together, they occurred less frequently in the MP group (3%) as compared to the DEX-containing groups (11%) (P=0.007), but also when the comparison was restricted to DEX alone (13%) (P=0.007). Deep venous thrombosis / pulmonary embolism was equally distributed among arms (3 to 5%). When combining all severe non hematological complications, the incidence was also lower in the MP group (16%) than in the DEX-containing groups (28%) (P=0.01), but also when the comparison was restricted to M-DEX (31%) and to DEX alone (27%) (P=0.01 and 0.05, respectively). A total of 14 patients had a solid tumor during trial follow-up (4, 4, 4 and 2 patients in the MP, M-DEX and DEX-IFN groups, respectively), direct cause of death in 6 patients.
Table 5. Severe non hematological toxicities in the IFM 95-01 trial analyzed by treatment allocation (No. of patients, %)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Total no. (n=488) (%)</th>
<th>MP (n=122)</th>
<th>M-DEX (n=118)</th>
<th>DEX (n=127)</th>
<th>DEX -IFN (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe pyogenic infections</td>
<td>59 (12)</td>
<td>12</td>
<td>22</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>- pulmonary</td>
<td>25 (5)</td>
<td>5</td>
<td>11</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>- septicemia</td>
<td>18 (4)</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>- other</td>
<td>16 (3)</td>
<td>5</td>
<td>6</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Haemorrhage (severe)</td>
<td>10 (2)</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Perforated diverticulum</td>
<td>8 (2)</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Psychiatric complications</td>
<td>13 (2.5)</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>8*</td>
</tr>
<tr>
<td>Diabetes (severe)</td>
<td>16 (3)</td>
<td>2</td>
<td>2</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>DVT**/ Pulmonary embolism</td>
<td>21 (4)</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Any severe toxicity</td>
<td>121 (25)</td>
<td>20</td>
<td>36</td>
<td>34</td>
<td>31</td>
</tr>
</tbody>
</table>

*including suicide in 1 patient ; **DVT; deep venous thrombosis

DISCUSSION

In a large randomized trial comparing MP, as the reference treatment in elderly newly diagnosed MM patients, to three different treatments including DEX (M-DEX, DEX and DEX-IFN), no difference in overall survival was evidenced between the four treatment groups, whereas response rate appeared to be significantly higher in patients receiving M-DEX than in those receiving other treatments and progression-free survival was significantly better in patients receiving M than in those receiving DEX without M. In addition, severe non hematological toxicities were significantly more frequent in patients receiving DEX regimens than in patients receiving MP, especially severe pyogenic infections in patients receiving M-DEX, and hemorrhage, perforated diverticulum, psychiatric complications or severe diabetes in those receiving a DEX-containing regimen.
At the time the IFM 95-01 trial was initiated, the MP regimen was still the reference treatment for elderly newly diagnosed MM patients, ineligible for high-dose therapy but DEX or DEX-containing regimens were considered of interest. Indeed, Alexanian et al. had reported a 43% response rate in newly diagnosed MM patients treated with DEX alone, which was only 15% below the response rate achieved with the VAD regimen with no differences in survival. The study was not randomized, consisting of 112 consecutive patients with a median age of 60 years (the youngest patient was 30 years of age) and a relatively short follow-up. In 88 patients who had failed to achieve response with induction chemotherapy, Salmon et al. had investigated the DEX-IFN regimen as a rescue treatment. These patients had a better average outcome in terms of survival than did patients responsive to the initial chemotherapy with a median survival of 48 months from start of DEX-IFN, providing a rationale for a large evaluation of DEX-IFN in newly diagnosed patients. In 1995 the M-DEX combination had not been evaluated in a randomized study, and only one recent publication has presented a comparison between MP and M-DEX.

The aim of the IFM 95-01 study was to compare, in elderly patients ineligible for high-dose therapy, MP, M-DEX, DEX alone and DEX-IFN. This study represents the largest randomized trial comparing MP to various DEX regimens before the availability of new drugs such as thalidomide, bortezomib or lenalidomide. It is of importance to consider that these patients were between 65 and 75 years of age and that the study was performed in 104 centers in France, Belgium and Switzerland, adequately reflecting an elderly unselected MM population referred to hospital in a recent period of time. Moreover, the follow-up was rather long for a clinical trial in MM, with a median of about 7 years.

The achievement of at least a partial response was significantly more frequent in the M-DEX arm (P < 0.001) (Table 2). Response rates at 6 months (and also at 12 months, data not shown) were similar in DEX without M and MP regimens (Table 2). A slight increase in
response rate could not be excluded between 6 and 12 months for MP (41 % at 6 months vs 50 %
at 12 months, data not shown), possibly reflecting the presence of few slow responders in the MP
arm. In the recent study reported by the Spanish PETHEMA group (170 patients, median age 74
years, 87 receiving MP and 83 M-DEX), the partial response rates at 6 months were similar to
those achieved in our study: 41 % in both studies for MP, 59 % and 70 % for M-DEX in the
PETHEMA study and the IFM 95-01 study, respectively. In both studies also, response rates
achieved by M-DEX were superior at 12 months to those achieved by MP 5.

The disease control achieved by DEX and DEX-IFN was clearly inferior to that achieved by
melphalan-containing treatments (MP and M-DEX) in terms of progression-free survival and
MM-related deaths in the first 3 months of treatment (Table 4 and Figure 1B). Of note is the fact
that 12/248 patients receiving DEX or DEX-IFN had MM progression and death in the first 3
months, whereas it was the case for only 1/240 patient receiving MP or M-DEX (P=0.003). Nine
of these early deaths occurred in patients treated with DEX-IFN and the possibility that IFN
could promote MM progression is some rare patients may not be ruled out. The progression-free
survival curves separated very early in a two by two pattern whether the patients received
melphalan or not (Figure 1B). The progression-free survival advantage obtained in patients
receiving melphalan did not translate in a better survival, as the overall survival was similar
among arms (Figure 1A). In fact, patients initially treated with DEX or DEX-IFN had a better
average outcome after the first progression (Figure 1C). Second line treatment consisted of
alkylating-agent based regimens in the vast majority of these patients, and these regimens
appeared able to rescue patients at relapse in the DEX and DEX-IFN arms (Table 3).

The IFM 95-01 provides the most complete data-base for DEX toxicity in elderly MM
patients. The severe non-hematological toxicities were significantly more frequent in all DEX-
containing arms (Table 5). The incidence of serious DEX complications was lower in the initial
report of Alexanian et al., but their patients were younger (median age 60 years vs 70 years in
the IFM 95-01 study), including some very young patients. DEX-related toxicity is in part age-related and our results are in line and extend the results in the recent PETHEMA study. Our 19% incidence (22/118 patients) of severe pyogenic infections in the M-DEX arm was similar to the 14% incidence of the PETHEMA study which considered also an elderly population. In addition, we found approximately 12% more severe non hematological complications in DEX-containing arms than in the MP arm, a result comparable to the more limited difference observed in the PETHEMA study (grade 3/4 toxicity during cycles 1-6 was 3% in the MP arm vs 12.5% in the M-DEX arm). Even when considering DEX alone or M-DEX, the toxicity was higher to the one observed with MP. Of note, in a recent ECOG study in elderly patients (median age = 65 years), DEX toxicity was also a concern, with 17% of patients having a grade ≥ 4 toxicity. The DEX-IFN arm had the same profile for DEX toxicity with a greater incidence of psychiatric complications and approximately one fourth of patients who had to stop IFN because of toxicity. The IFM 95-01 trial also provides useful information regarding the incidence of deep venous thrombosis (DVT) in the context of MP or DEX-containing regimens, before the use or the addition of thalidomide. Overall, we had a 4% incidence of DVT and this incidence was similar among the different treatments. Recent results from ECOG also found a 3% incidence of DVT using DEX alone.

Taking into account efficacy and toxicity results, we concluded that in the context of the IFM 95-01 trial, the standard melphalan-prednisone remained the best treatment choice in elderly patients. It does not exclude that the use of DEX could be an option in individual patients and selected situations such as renal failure, cord compression or reduced blood count values. The addition of IFN to DEX was of no benefit in our trial, as also shown recently with maintenance IFN in the US Intergroup trial. In the recent period, DEX containing regimens have been often designed for transplant candidates to avoid melphalan exposure prior to stem cell harvest, but have been extrapolated to the non transplant population without any convincing
data. The results of the IFM 95-01 trial are useful to design future combinations to innovative
drugs, such as thalidomide, bortezomib or lenalidomide. These new drugs will possibly add
efficacy to the conventional treatment, but will also add their own toxicity. Due to the toxicity of
DEX or DEX-containing regimens in elderly patients, the combination of these innovative drugs
with melphalan should, in our opinion, be favored.
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References


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