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Randomized Trial of α-Interferon or Dexamethasone as Maintenance Treatment for Multiple Myeloma

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In order to assess the role of α-interferon or dexamethasone as maintenance therapy for multiple myeloma, 172 consecutive, previously untreated patients with disease of low or intermediate tumor mass received primary therapy with oral melphalan and intermittent, high-dose dexamethasone (MD), repeated monthly. Within 5 months, 84 responding patients were assigned at random to maintenance treatment with α-interferon (3 mU s.c. 3 × weekly) or dexamethasone (20 mg/m² p.o. each morning for 4 days) repeated monthly until relapse. Upon relapse, MD was resumed for 2 cycles and second responses were maintained with 4-day courses of melphalan–dexamethasone until second relapse. Initial response was achieved in 88 patients (51%) after a median 0.7 month and no more than 3 courses of MD, a frequency of response similar to that observed previously with dexamethasone alone. There were identical median remissions of 10 months with interferon or dexamethasone, both maintenance regimens being associated with infrequent, mild, and reversible side effects. Significantly more patients responded again to resumption of MD after disease relapse to interferon (82%) than to dexamethasone (44%) (*P* = 0.001). The median remission from randomization to melphalan-resistant second relapse was 32 months for patients maintained initially on interferon compared to 19 months for those on dexamethasone (*P* = 0.01). These findings supported an advantage for interferon in remission maintenance by increasing the frequency of tumor recontrol with later treatment that included dexamethasone. Am. J. Hematol. 65:204–209, 2000.

Key words: α-interferon; dexamethasone; multiple myeloma

INTRODUCTION

Many treatments have been useful for patients with multiple myeloma (MM). Several studies have shown no advantage for combinations of multiple alkylating agents with or without a glucocorticoid, in comparison with melphalan–prednisone [1–3]. Vincristine–doxorubicin by continuous infusion with intermittent dexamethasone (VAD) has not improved the survival of newly diagnosed patients [4]. Many other treatments have been studied, including more intensive programs supported by autologous stem cell transplantation. One such study described a significantly longer survival than that with standard therapy for patients less than 60 years old, but older patients and those with disability or a serious complication were excluded because of excessive risk [5]. Dexamethasone in repeated high dose represents the most effective single agent for MM and has induced a high frequency and rapid onset of response [6], but the addition of α-interferon did not improve outcome among newly diagnosed patients [7]. We combined oral melphalan at standard dose with high-dose pulse dexamethasone as primary treatment for patients with multiple myeloma of low or intermediate tumor mass.

Maintenance therapies for responding patients remain controversial. Most controlled studies have shown a modest prolongation of disease response with α-interferon without an improvement of survival [8–14]. Such treatment may have side effects and is inconvenient and costly. In order to assess the value of single-agent dexamethasone or interferon in maintenance of response, we prospectively assigned 84 responding patients at random to treatment with one or the other agent.

MATERIALS AND METHODS

Patients and Drug Regimens

Between July 1991 and August 1997, MD was given to 172 consecutive, previously untreated patients with symptomatic MM of low or intermediate tumor mass. The median age was 58 (range 29–85), hemoglobin was

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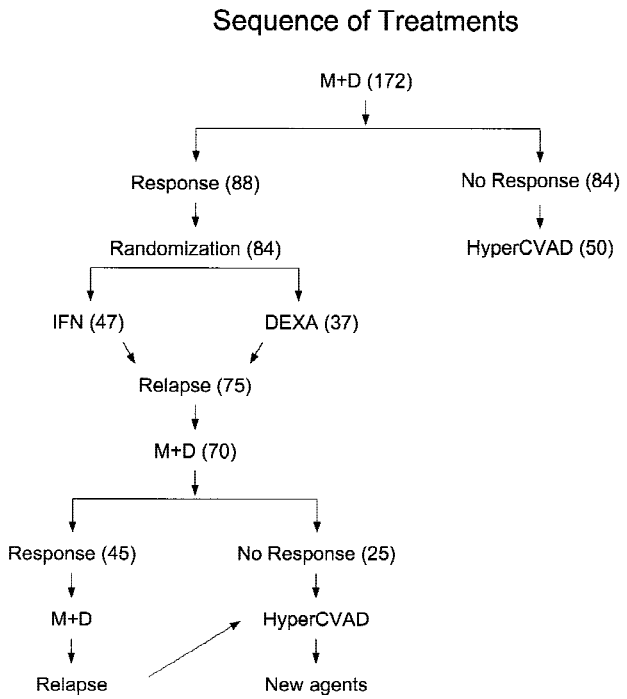

Fig. 1. Sequence of treatments for 172 previously untreated patients with symptomatic multiple myeloma of low or intermediate tumor mass. M + D, melphalan–repeated dexamethasone; IFN, α-interferon s.c. t.i.w.; DEXA, dexamethasone p.o. for 4 days/month; HyperCVAD, high-dose cyclophosphamide, vincristine, doxorubicin, dexamethasone. Numbers in parentheses indicate the number of patients.

<10.0 g/dl in 22%, creatinine >2.0 mg/dl in 6%, and B_2M >3.0 mg/L in 52% of patients. (Ninety-three other patients with high tumor mass, as defined by serum calcium >11.5 mg/dl or hemoglobin <8.5 g/dl, were excluded in order to receive more intensive treatment.) All patients who received MD were randomized to maintenance with interferon or dexamethasone as soon as clinical response was confirmed (Fig. 1). Melphalan was given in a dose of 7 mg/m^2 each morning for 4 days beginning on day 1 and dexamethasone in a dose of 20 mg/m^2 each morning for 4 days beginning on days 1, 9, and 17 with dietary salt restriction; after a 14-day rest, the combined treatment was repeated. In view of our data on the rapid response with pulse dexamethasone [6], no more than three courses of MD were prescribed.

Within 5 months of initial treatment, 84 responding patients received either α-interferon (IFN) 3 mU s.c. 3 × weekly (interferon α-2b, recombinant, Intron-A) or dexamethasone (DEXA) 20 mg/m^2 each morning for 4 days each month as soon as remission could be confirmed. The study was intended to provide independent assessments of two programs for prolonging remission conducted in parallel. Four responding patients were not eligible for response maintenance because they received a myeloablative consolidation treatment supported by autologous blood stem cell transplantation [15].

All but 5 patients maintained on IFN or DEXA have relapsed; of these 75 patients, 70 have been retreated and evaluated on the same program of MD to which they had responded initially (Fig. 1); for those whose myeloma responded again, maintenance consisted of 4-day courses of melphalan–dexamethasone each month until second relapse.

Staging and Clinical Response

The diagnosis of MM was based on standard criteria in symptomatic patients; all showed bone marrow plasmacytosis of more than 10%, all but 5 patients showed a monoclonal globulin on serum or urine electrophoresis, and 81% had lytic bone lesions. Low tumor mass required normal serum calcium, hemoglobin >10.5 g/dl, and serum myeloma protein <4.5 g/dl; the remaining patients with intermediate tumor mass had either hemoglobin of 8.5–10.5 g/dl, serum myeloma protein ≥4.5 g/dl, or both. Clinical response was defined as at least a 75% reduction of serum myeloma protein production, a 95% reduction of Bence Jones protein, *and* reduction of marrow plasmacytosis to less than 5% [16]. Response duration was calculated from the onset of maintenance to the first evidence of rising myeloma protein by at least 25%, a new bone lesion, or an increase of marrow plasmacytosis to >10%. Four patients died during the first 2 months and were considered unresponsive; three patients died later of diseases unrelated to multiple myeloma, all with responsive disease and assigned to interferon.

Statistical Analyses

Response duration with IFN or DEXA maintenance was the primary endpoint; other endpoints were the time to melphalan resistance, duration of second remission, and survival. All time intervals were measured from the start of maintenance therapy, except for second response duration. The two patients who died in first remission and the other who died in second remission were considered as failures at the time of death. Patients were considered melphalan-resistant upon relapse to the second response, except for those patients who did not achieve second response, in which case relapse to first response defined the time of melphalan resistance. The Kaplan–Meier method was used to estimate distributions; comparisons of remission and survival used the log rank test [17], and all confidence intervals are of 95% range.

RESULTS

Frequency of Response

The myeloma responded to primary therapy with MD in 88 patients (51%, CI 43–59%), a frequency similar to

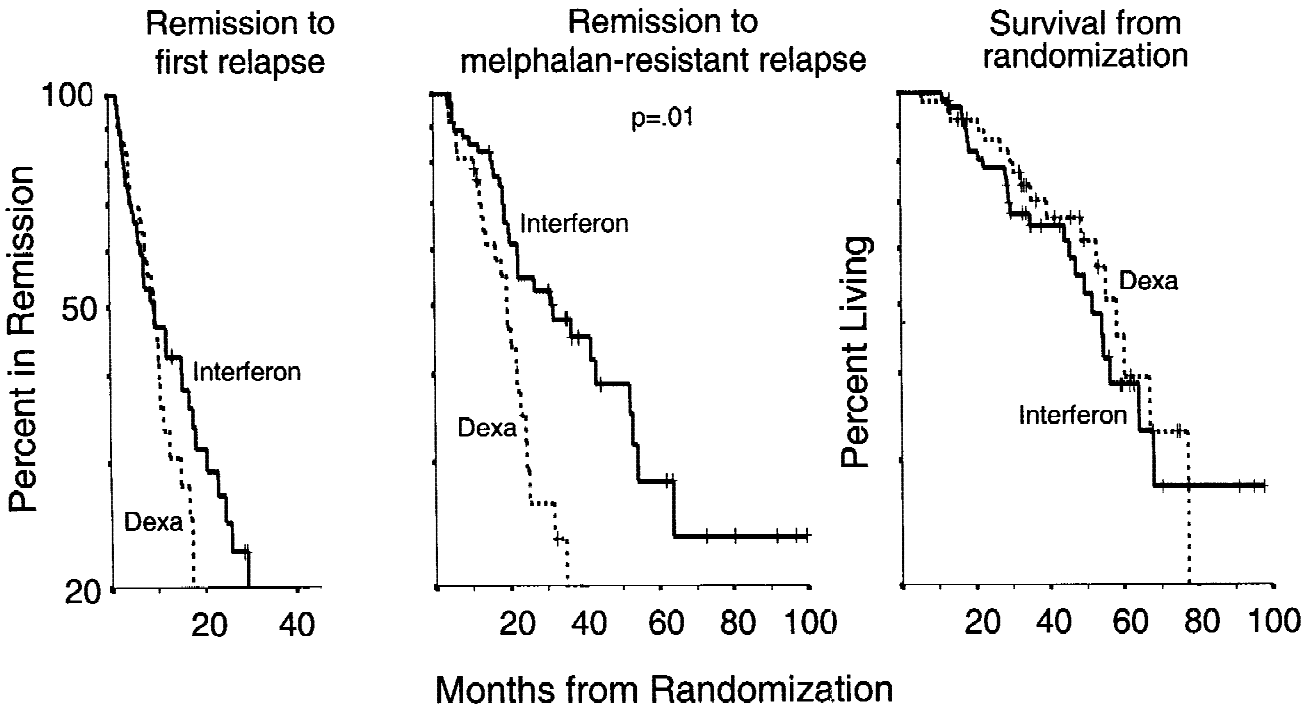

Fig. 2. (Left panel) Similar durations of first remission for 84 responding patients randomized to α-interferon or dexamethasone (dexa). (Middle panel) Longer duration of remission from randomization to melphalan-resistant relapse for patients maintained on interferon. (Right panel) Similar survival from randomization for patients randomized to interferon or dexamethasone.

that of 46% for comparable patients treated previously with dexamethasone alone [6]. The rapidity of response was assessed from serial changes in IgG or IgA myeloma protein production [16]. Among patients with responsive disease, the median time to response was 0.7 month (range 0.2–4.0 months) and was confirmed within 2 months in 89% of responding patients. Serum myeloma protein disappeared on immunofixation studies in 5% of all patients. For patients with disease unresponsive to induction therapy, an intensive program of hyperCVAD therapy was given to 50 patients, of whom 10 responded for a median 16 months [18]; these patients were considered too few and the gains too limited to affect the analysis of survival; the remaining 34 patients received intermittent chemotherapy with an oral alkylating agent–glucocorticoid combination in standard doses until death. The median survival for all 172 patients was 48 months, similar to that described previously for comparable patients treated with VAD or dexamethasone [4,6,7].

Response Duration and Survival

Responding patients began maintenance treatment after a median 2.5 months of initial therapy (range 0.7–4.9 months) (Fig. 1). The slight difference in number of patients who received interferon or dexamethasone was attributed to the coincidental higher response rate among patients destined to receive interferon rather than dexamethasone. For patients on interferon or dexamethasone, the median age was similar (59 vs. 56), as were the frequencies of low tumor mass (57% vs. 62%) and B_2M above 3.0 mg/l (46% vs. 53%); the frequency of males was identical at 51%. The median remissions of responding patients maintained on IFN or DEXA were identical at 10 months (Fig. 2, left panel). The median survival times from start of maintenance were also similar at 52 months with interferon and 58 months with dexamethasone (Fig. 2, right panel).

Relapse and Disease Recontrol

Relapse has occurred in 75 of 84 patients maintained in first response, of whom 45 achieved a second response after retreatment with MD. The frequency of disease recontrol was significantly higher after prior treatment with IFN (82%, CI 66–92%) than with DEXA (44%, CI 26–62%) ($P < 0.001$). When they occurred, the durations of second response with MD maintenance tended to be longer after prior interferon (median 15 months) than after dexamethasone (median 10 months), but the sample size was insufficient to define superiority for either group. Among 45 patients with recurrent disease who responded again, the second response was at least 3 months shorter than the first response in 7 patients, no more than 3 months shorter or 5 months longer than the first response in 9 patients, and more than 5 months

longer than the first response in 26 patients; 3 other patients remain in second response so that differences could not be compared. The duration from randomization to melphalan-resistant relapse was significantly longer with interferon (median 32 months) than with dexamethasone (median 19 months) ($P = 0.01$) (Fig. 2, middle panel).

Toxicity

Most patients treated with MD had short periods of flushing, insomnia, and mild fluid retention attributed to repeated dexamethasone, but less than 10% had aggravation of diabetes that required insulin or severe fluid retention that required a diuretic. Two patients developed gastrointestinal bleeding from occult duodenal ulcers that was controlled medically. None developed the candidiasis, herpes simplex lesions, or quadriceps weakness that have occurred in approximately 5% of patients treated previously with long-term dexamethasone [6,7]. No patient treated with MD or dexamethasone required hospitalization for septic complications due to neutropenia or to infections from a central venous catheter in contrast to 27% of patients treated previously with VAD [4].

The principal side effects with interferon were fatigue (39%), anorexia, difficulty concentrating, and achiness (4% for each), and skin rash in one patient, all of mild degree. In absence of side effects, the dose was increased to 4 mU in 8 patients (17%); when side effects detracted from a normal quality of life, the dose was reduced to 1.5–2.0 mU in 17 patients (36%), including 10 of 13 patients older than 65; the remaining 22 patients continued on 3 mU thrice weekly. Common side effects with maintenance dexamethasone were several days of irritability and/or insomnia (25%), fatigue (19%), fluid retention (17%), hypertension (6%), mouth sores (6%), indigestion (3%), and hyperglycemia that required insulin (3%), all of mild degree. Dexamethasone dose was maintained in all but 13 patients (35%) who received a lower dose of 12–15 mg/m^2 for 4 days each month, a reduction not more common among older patients. Interferon was discontinued in one patient after 11 months because of recurrent skin rash (despite substitution of interferon α-2a, recombinant), and dexamethasone was discontinued in one patient after 10 months because of acute pancreatitis.

Association of Other Factors With Outcome

Despite the small number of patients, we assessed several prognostic factors for a possible adverse effect on duration of first response and on the likelihood and duration of second response; these included age >60 years, Hgb <10.5 g/dl, serum B_2M >3.0 mg/l, intermediate tumor mass, and slow onset of first response. There was no evidence of major differences in outcomes associated with these factors.

DISCUSSION

Many treatments have been effective in newly diagnosed patients with MM, including combinations of one or more alkylating agents with a glucocorticoid, the VAD regimen, or intermittent dexamethasone alone [1–6]. Among comparable patients, the response rate with VAD was approximately 15% higher than that with dexamethasone, but survival times were similar and VAD was associated with more toxicity [4]. Limited therapy with MD induced a response rate and survival similar to those after many months of VAD or dexamethasone, but with a shorter exposure to potential side effects [4,6,7]. The rapidity of disease control permitted maintenance therapy within 5 months in all responding patients and after only two courses of treatment in 89% of patients.

Long-term treatment with melphalan was avoided in order to preserve hematopoietic and immunologic function, to retain sensitivity of the myeloma to later retreatment, and to reduce the potential risk of secondary leukemia. This strategy also permitted early recognition of unresponsive patients who qualified for more intensive regimens before occurrence of a serious complication and allowed more successful mobilization of blood progenitor cells for myeloablative therapy when that procedure was indicated [15]. Based on the rate of myeloma protein change, additional courses of treatment were unlikely to increase the response rate to a major degree but might have reduced the myeloma further in some responsive patients. Yet, the similar response rate and survival in comparison with those achieved previously after longer periods of VAD or dexamethasone suggested that no more than the minimum number of courses required to induce remission was necessary for most patients. Such a strategy of limited but effective primary therapy, followed by no or limited maintenance therapy, has been useful for patients with other low-grade lymphoproliferative disorders that are considered incurable. For example, limited therapy with a nucleoside analogue has induced repeated long-term control in many patients with hairy cell leukemia, Waldenström's macroglobulinemia, or chronic lymphocytic leukemia [19–21].

The optimum program of response maintenance for MM remains controversial. In 5 controlled studies, the median response was prolonged by 4–12 months with α-interferon in comparison with comparable patients who received no treatment [8–12], but no benefit was observed in 2 other studies [13,14]. When one considers the wide confidence intervals of all studies, the median response appeared to be 6 months longer with interferon than with no treatment. Most reports have failed to detect any improvement in survival, probably because disease relapsing on interferon or no treatment was usually recontrolled or stabilized upon resumption of standard chemotherapy and later use of more intensive therapies.

Unlike previous multicenter trials that excluded as many as 27–38% of responding patients and enrolled others after more than 1 year of initial therapy, with the consequent selection of patients with uncertain prognoses [9,11,13], all of our responding patients were randomized within 5 months of initial treatment. Eligibility was restricted to patients with low or intermediate tumor mass in order to exclude patients with more advanced disease in whom disease responses are often short, the morbidity upon relapse high, and for whom myeloablative consolidation therapy seems preferable [15]. No major differences were observed in response and survival times with interferon or dexamethasone, but more frequent disease recontrol occurred after prior maintenance with interferon. While these findings supported a useful role for both interferon and dexamethasone in primary remission maintenance, the more frequent tumor recontrol after interferon provided an advantage over the simplicity and lower cost of dexamethasone.

When the disease relapsed despite either maintenance, recontrol was achieved in many patients and sustained for a longer period than the first response. Tumor resistance to resumption of melphalan–dexamethasone was more frequent after dexamethasone perhaps because repeated exposures led to the earlier acquisition of resistance to this agent. Also, the longer second remission with maintenance may have resulted from the limited exposure to initial melphalan and longer preservation of disease sensitivity later in the disease course. However, the progressive resistance of the myeloma to retreatment with either maintenance reflected the inexorable growth with time of resistant subclones as shown previously with VAD and more intensive therapies for resistant disease [18,22,23]. The failure of melphalan to improve on the initial response rate observed previously with dexamethasone [6], and the longer second response with later melphalan maintenance, indicated that further studies would be useful on the role of later, rather than early, use of an alkylating agent.

A recent multicenter study indicated a longer response for patients whose disease had responded to VAD and who were maintained on both interferon and alternate-day prednisone, in comparison with interferon alone [24]. In contrast to our study, patients with high tumor mass were included, received primary treatment for as long as 9 months, and qualified for maintenance despite less than a 75% reduction of tumor mass. The frequency and duration of second response with resumption of an alkylating agent upon relapse were not assessed. Both studies supported the value of α-interferon and/or a glucocorticoid for response maintenance in patients with multiple myeloma. Whether a combination of interferon with dexamethasone has outcomes and side effects similar to interferon–prednisone requires further study, but there is potential for more frequent tumor resistance upon later retreatment with either program.

Recent randomized studies have concluded that early myeloablative treatment supported by autologous stem cells produced a longer survival than continued standard treatment, but the specific categories of patients who were most likely to benefit were unclear [5]. The risks of such therapy are higher for older patients (who are usually excluded from clinical trials) and those with poor performance or with serious cardiac, respiratory, or renal diseases. Such patients who have responded well to primary treatments but are unsuitable for intensive consolidation therapy should be considered for a strategy of maintenance similar to that described here. With frequent monitoring of side effects, prevention of anticipated complications, and rational dose reductions, all patients were treated in an acceptable manner regardless of age or disability.

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