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A Comparison of Polychemotherapy and Melphalan/Prednisone for Primary Remission Induction, and Interferon-alpha for Maintenance Treatment, in Multiple Myeloma. A Prospective Trial of the German Myeloma Treatment Group*

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406 untreated multiple myeloma patients of stage I (n = 54), II (n = 148) and III (n = 204) were enrolled in the trial. 51/54 stage I and 60/148 stage II patients were asymptomatic and followed without treatment until disease progression (progression free survival: 60% after 4 years for stage I versus 50% after 1 year for stage II). Symptomatic patients of stage I (n = 3/54) and II (n = 88/148) presenting with tumour progression, received melphalan 15 mg/m^2 intravenously (i.v.) and prednisone 60 mg/m^2 oral days 1–4 (MP). Stage II disease remission rate was 59%, and 50% tumour related survival (TRS) was 59 months. Stage III patients were randomised to receive MP or VBAMDex (vincristine/BCNU/doxorubicin/melphalan/dexamethasone) treatment. 43% of MP treated patients responded compared with 64% of the VBAMDex group. 50% TRS was 36 months in both groups without a detectable difference. 117 responders of stage II and III with stable disease were randomised to receive either IFN-α (5 × 10^6 IU, subcutaneous (S.C.) 3 times per week) or no maintenance treatment. The relapse rate in both groups was 50% after 13 months. No survival benefit for IFNα treated patients was observed (50% TRS: 45 months).

INTRODUCTION

PATIENTS WITH multiple myeloma (MM) are heterogeneous in terms of symptoms, complications and survival prognosis. Treatment is palliative and requires an individualised approach involving chemotherapy, irradiation, surgery, and supportive care. Chemotherapy with intermittent melphalan and prednisone (MP) has remained the standard treatment for primary remission induction [1], since no other drug combination has convincingly been shown to induce better survival rates so far [2]. In a phase II study, high remission rates have been shown for the multidrug combination vincristine, BCNU, doxorubicin melphalan and dexamethasone (VBAMDex) both in untreated and in pretreated MM patients [3]. We therefore carried out a prospective trial to test VBAMDex versus MP in stage III MM patients.

Since currently used standard chemotherapy schemes are palliative rather than curative, remission duration is comparatively short in MM. Most patients experience their first relapse within the first year after completing induction chemotherapy, if no maintenance treatment is given. However, although maintenance chemotherapy significantly postpones relapses, a survival benefit is not achieved [4]. Interferon-α (IFN-α) produces a response rate of 20% when used as a single agent in MM [5]. Therefore, the efficacy of this cytokine has been tested as maintenance treatment in the present study.

During the course of MM, cytokinetically quiescent phases called smoldering myeloma, or plateau phases, without measurable tumour progression can be observed [6, 7]. We have therefore posed the question how many MM patients of stages I and II might be in such a plateau phase at the time of diagnosis, and have thus investigated the risk of disease progression of untreated stage I and II MM patients after diagnosis under continuous observation. The combined results of these studies are reported in this paper.

PATIENTS AND METHODS

Patients

Between 1988 and 1991, 406 untreated MM patients with informed consent were recruited by six university hospitals and 19 local hospitals located in the Federal Republic of Germany. Follow-up data were available until December 1993. The diagnosis was made if at least two of the following criteria were found: > 15% bone marrow infiltration by malignant plasma cell, M-component in the serum and/or urine, lytic bone lesions. The patients were staged at diagnosis using the Durie/Salmon classification [8] based on tumour cell mass (TCM) calculations [9]. The characteristics of the patients including labelling index (LI) and grading of the plasma cells determined in bone marrow biopsies and/or smears [10, 11] are shown in Table 1. 54 patients had stage I MM, 148 had stage II and 204 patients had stage III MM. Mean observation time was 37 months in stage I, 34 months in stage II, and 25 months in stage III.

Design of the trial

The trial protocol was approved by the ethics committee of the Medizinische Hochschule Hannover. Asymptomatic (no bone pain, no symptoms due to anaemia, no hyperviscosity) MM patients of stage I and II were followed without any treatment. When signs of progressive disease (for definition see below) occurred, these patients were given melphalan/prednisone (MP) chemotherapy (for schedules see Table 2). Patients of stage III were treated at once and, after randomisation, received either MP or VBAMDex polychemotherapy. In responding patients, chemotherapy cycles were repeated until no further TCM reduction was observed during the last 2 months (i.e. two cycles MP or one cycle VBAMDex).

Patients with stable disease or remission after chemotherapy induction were randomised to receive either IFNα or no maintenance treatment. When relapsing, these patients were treated with the initial chemotherapy schedule again.

Patients primarily resistant to MP or in resistant relapse received VBAMDex polychemotherapy. VBAMDex resistant patients were individually treated with different experimental regimens.

IFNα binding antibodies were measured in serum samples taken before and after the maintenance phase from 35 IFN-treated MM patients and from 42 patients of the no maintenance group by an ELISA technique [12].

Definition of response

Response to treatment was evaluated by the GMTG criteria which, in an earlier trial, proved to be of prognostic significance [13]. Changes of the individual TCM were determined by serum myeloma protein concentrations [9]. A TCM reduction of more than 25% was defined as remission, an increase of the TCM of more than 25% above the initial value was defined as progressive disease, and a relapse was stated if a > 25% increase occurred after successful remission induction. Minor variations (± 25%) of the TCM were designated as no change. Additionally, in all patients and particularly in Bence Jones and non-secretory MM, the response was estimated by clinical parameters, i.e. new bone lesions, appearance or disappearance of hypercalcaemia, changes in bone marrow infiltration.

Statistical analyses

Calculations of survival and response duration were carried out using the method of Kaplan and Meier [14]. Overall survival (OAS) was differentiated from tumour-related (TRS) survival [15]. For OAS, all cases of death were defined as events. For TRS, cases of death due to disorders others than MM were used as censored data. Each patient was considerd as alive at the time of his last evaluation, if death had not occurred. Differences in survival and response duration between patients' groups were calculated by the generalised Wilcoxon and the log rank tests.

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Table 1. Patients' characteristics (n = 406)

	Stage I	Stage II		Stage III	
		No initial therapy	Initial MP	MP	VBAMDex
n	54	60	88	99	105
Male (%)	44	43	51	55	54
Female (%)	56	57	49	45	46
Mean TCM ($\times 10^{12}/m^2$)	0.48	0.83	0.94	1.46	1.46
Myeloma protein (%)					
IgG (%)	64	69	70	56	57
IgA (%)	32	22	22	25	28
IgD (%)	0	0	1	2	0
Biclonal (%)	2	4	0	0	0
None (%)	2	5	7	17	15
B.J.-protein (%)					
None	70	55	42	32	29
Kappa	17	20	39	41	44
Lambda	13	25	19	27	27
Histological grading (n = 240)					
n	33	32	48	63	64
Marschalko (%)	88	66	56	38	40
Small cell, cleaved, polymorphous (%)	12	31	29	35	36
Asynchronous and blastic type (%)	0	3	15	27	24
Labelling index (n = 71)					
n	15	14	14	28	
Mean (%)	0.4	0.4	1.6	2.9	
Range (%)	0.0–2.4	0.0–1.0	0.0–5.2	0.0–44.0	

MP, chemotherapy with melphalan and prednisone.
VBAMDex, chemotherapy with vincristine, BCNU, doxorubicin, melphalan & dexamethasone.
TCM, tumour cell mass.

Table 2. Chemotherapy schedules

MP
Melphalan 15 mg/m² i.v., day 1
Prednisone 60 mg/m² oral, days 1–4
Repeated every 29 days
VBAMDex
Vincristine 1 mg/m² i.v. days 1, 15, 29, 43
BCNU 40 mg/m² i.v. day 1
Doxorubicin 15 mg/m² i.v. days 1, 15, 29, 43
Melphalan 7 mg/m² i.v. days 1, 15, 29, 43
Dexamethasone 40 mg/m² i.v. days 1–4, 15–18, 29–32, 43–46
Repeated every 57 days
IFNα maintenance
5×10^6 IU recombinant IFNα2b (Intron A^R) s.c. three times weekly until relapse. Intron A^R was kindly provided by ESSEX PHARMA GmbH, Munich, Germany

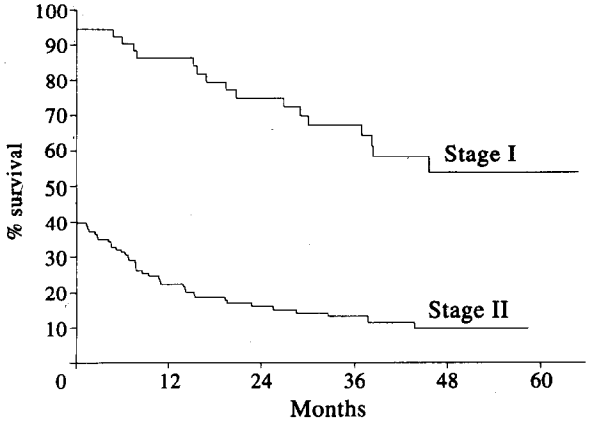

Figure 1. Unmaintained stable disease from diagnosis until start of induction chemotherapy in stage I and II MM patients.

The chi squared test was applied for analysing differences in response rates between groups.

RESULTS

Plateau phase at diagnosis

Stage I patients had the lowest LI, and a Marschalko plasma cell type in 88% (Table 1), associated with a good prognosis [10]. 51/54 stage I MM patients were asymptomatic at diagnosis, and thus remained untreated initially. During the subsequent 4 years of observation, only 40% of these patients had tumour progression and therefore received chemotherapy (Figure 1) In stage II MM, 88/148 patients were symptomatic or had progressive disease at diagnosis, and therefore received MP treatment immediately. An asynchronous or blastic plasma cell morphology, indicating worse prognosis as well as a higher LI, occurred more frequently among these patients than among 60/148 stage II patients (Table 1) who were categorised as plateau phase MM at diagnosis. Half of the latter group of patients showed a progression free period of more than 1 year (Figure 1).

Response rates, duration and toxicity of chemotherapy induction

90/126 stage II patients who were referred for MP treatment were evaluable for response (Table 3). 59% achieved a remission

Table 3. Response to chemotherapy induction

	stage II	stage III		
	MP	MP		VBAMDex
n	90	85		87
Remission (%)	59	43		64
Stable disease (%)	18	16	$P = 0.01$	10
Progressive disease (%)	21	32		14
Early death (%)	1	9	n.s.	12

and 18% stable disease with no change in the TCM. 204 stage III patients were randomised for either MP or VBAMDex induction treatment. The characteristics of both groups were not statistically different (Table 1). 32 patients were not evaluable for response (loss of follow up or missing records: $n = 17$; inadequate modifications of therapy or missing complience of the patients: $n = 15$). 172 patients were therefore evaluable for response (Table 3); the remission rate was higher ($P = 0.01$) in the VBAMDex group (64%) than in the MP group (43%).

In non-progressing patients, the mean duration of induction chemotherapy was 7 months (range 2—19 months), no significant differences being observed between stages II and III, MP or VBAMDex chemotherapy, or among patients further randomised into IFNα maintenance or no maintenance treatment arms. Early deaths did not occur significantly more often in the VBAMDex group of stage III MM (Table 3), although the toxicity of the former scheme was somewhat higher as expected from the additional chemotherapeutics given to VBAMDex treated patients (Tables 4, 5).

Survival

50% OAS for all patients (stages I, II, III) was 39 months compared with 45 months for 50% TRS (log rank: $P < 0.05$, Wilcoxon: $P < 0.03$). During the observation time, 4/54 stage I patients died from MM, whereas 7/54 succumbed to other diseases not related to MM. Therefore, TRS of stage I MM patients was 80% at 60 months. 50% TRS of stage II patients was 59 versus 36 months in stage III (Figure 2). Patients of stages II and III with asynchronous or blastic plasma cell morphology and/or platelets < 150 000/μl at diagnosis represented a high risk group [13] with a 50% TRS of 26 months (Figure 3). The 50% TRS of MP or VBAMDex treated stage III MM patients' groups did not differ significantly (Figure 4). This was also true, if patients over ($n = 83$) and below ($n = 121$) the age of 65 years were analysed separately.

IFNα maintenance versus no maintenance treatment

After chemotherapy induction 117 patients were randomised for IFNα maintenance treatment or observation only. The two groups were comparable in terms of response to induction chemotherapy, duration of induction treatment, and IgA and/or Bence Jones MM (Table 6). In 12/52 patients, the intended dose of 5×10^6 IU recombinant IFNα 3 times weekly had to be reduced to a mean dosage of 3.14×10^6 IU 3 times weekly due to toxicity (Table 7). Side effects of IFNα required termination of treatment in 2 patients. 50% relapse free survival was 13 months after induction of first remission in both IFNα treated and untreated patients (Figure 5). No survival benefit (TRS or OAS) has been observed so far (Figure 6). Analyses of subgroups of patients, as defined by the features indicated in Table 5, did not reveal any subgroup showing an advantage with respect to OAS, TRS, or relapse free survival for IFNα maintenance treatment. In the sera of 7/35 IFNα treated and 1/42 untreated MM patients low titres (< 250 IBU) of IFNα binding antibodies could be detected.

Table 4. Cumulative dose of chemotherapy needed for first induction treatment (mean dose/MM patient)

			melphalan	prednisone
MP (158 patients evaluable)			76 mg/m²	1296 mg/m²
VBAMDex (48 patients evaluable)				
vincristine	BCNU	doxorubicin	melphalan	dexamethasone
8 mg/m²	97 mg/m²	131 mg/m²	63 mg/m²	980 mg/m²

Table 5. Toxicity of chemotherapy in stage II and III multiple myeloma patients (the maximum toxicity which was observed in each patient during induction therapy was noted)

Toxicity/ WHO-grade	0	1	2	3	4
		VBAMDex (stage III, $n = 88$)			
Haemoglobin	19	24	29	14	2
Leucocytes	8	8	32	29	11
Platelets	60	15	5	4	4
Hair loss	37	19	19	13	0
Neurotoxicity	43	32	9	3	1
		MP (stage III, $n = 84$)			
Haemoglobin	27	26	18	11	2
Leucocytes	21	15	28	15	5
Platelets	65	6	5	4	4
Hair loss	76	5	2	1	0
Neurotoxicity	80	4	0	0	0
		MP (stage II, $n = 90$)			
Haemoglobin	44	26	13	6	1
Leucocytes	21	24	24	17	4
Platelets	64	14	5	5	2
Hair loss	84	5	1	0	0
Neurotoxicity	89	1	0	0	0

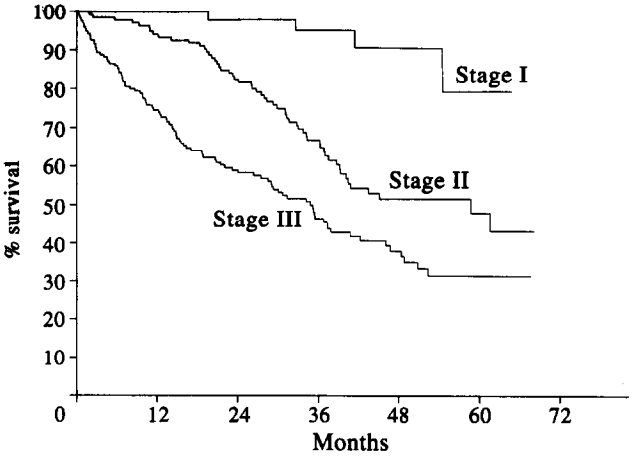

Figure 2. Survival (TRS) of MM patients ($n = 406$) stratified by the Durie/Salmon classification (log rank: $P < 0.0001$, Wilcoxon: $P < 0.0001$).

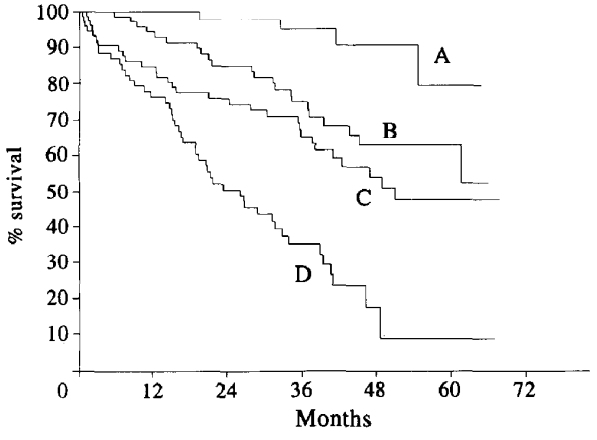

Figure 3. Survival (TRS) of MM patients (n = 283) stratified by the GMTG classification [13]. (A: stage I, n = 54; B: stage II and absence of risk factors, n = 72; C: stage III and absence of risk factors, n = 78; D: stage II or III *and* presence of risk factors, i.e. platelets <150 000 and/or asynchronic/blastic plasma cell morphology, n = 79; log rank: $P < 0.0001$, Wilcoxon: $P < 0.0001$).

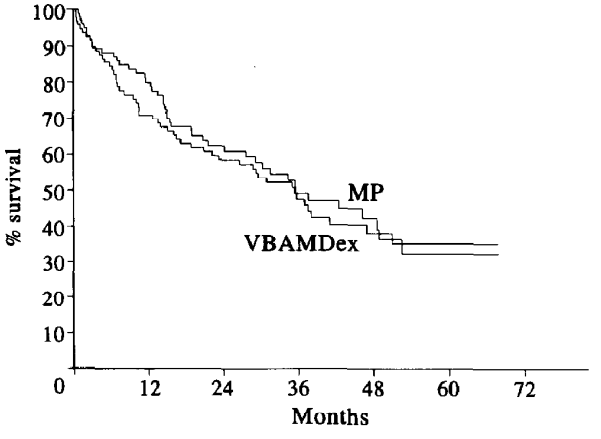

Figure 4. Survival (TRS) of stage III MM patients randomised for MP (n = 99) or VBAMDex (n = 105) chemotherapy induction (n.s.).

Table 6. Characteristics of patients randomised for IFNα or no maintenance treatment

	IFNα maintenance	No maintenance
All (n = 117)	52	65
> 75% TCM reduction to induction CT	31%	40%
> 50% TCM reduction to induction CT	50%	53%
> 25% TCM reduction to induction CT	61%	67%
IgA and/or Bence Jones MM	36%	38%
> 7 months induction CT	63%	58%

CT, chemotherapy.

DISCUSSION

Approximately 15% of MM patients of stage I and II are asymptomatic, so that the diagnosis is made by chance, for example, when an unexplained elevated erythrocyte sedimentation rate or a mild anaemia initiate a detailed laboratory investigation [1, 16]. Similarly, we found 25% of all patients in this study to be asymptomatic at the time of diagnosis (51 stage I and 60 stage II MM patients, Table 1). Both groups were followed prospectively without primary chemotherapy until progressive MM was ascertained. After 4 years, 60% of stage I patients still remained unchanged, i.e. were considered in plateau phase or smoldering MM (Figure 1). Even in stage II, one half of the initially asymptomatic patients were still asymptomatic after 1 year, and 10% were still asymptomatic after 4 years thus not requiring induction chemotherapy. In a recently reported prospective trial testing initial versus deferred

Table 7. Toxicity of IFN-α maintenance therapy in MM patients (n = 52; the maximum toxicity which was observed in each patient during therapy was noted)

Toxicity/WHO-grade	0	1	2	3	4
Haemoglobin	27	13	11	1	0
Leucocytes	22	9	12	8	1
Platelets	39	4	8	0	1
Hair loss	46	5	1	0	0
Fever	33	10	6	3	0
Fatigue	46	5	1	0	0

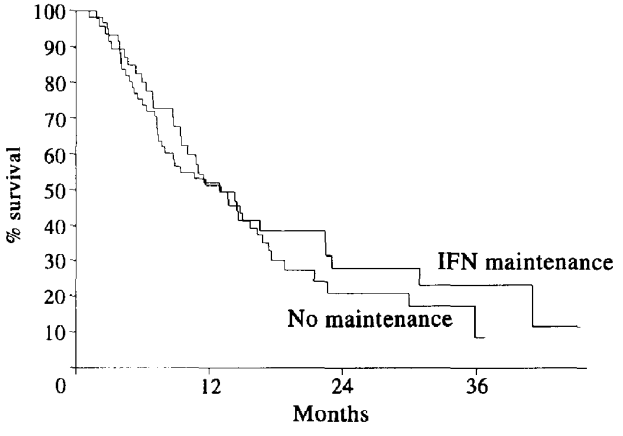

Figure 5. The effect of IFNα maintenance treatment on duration of remission after induction chemotherapy (IFNα maintenance, n = 52; no maintenance, n = 65; n.s.).

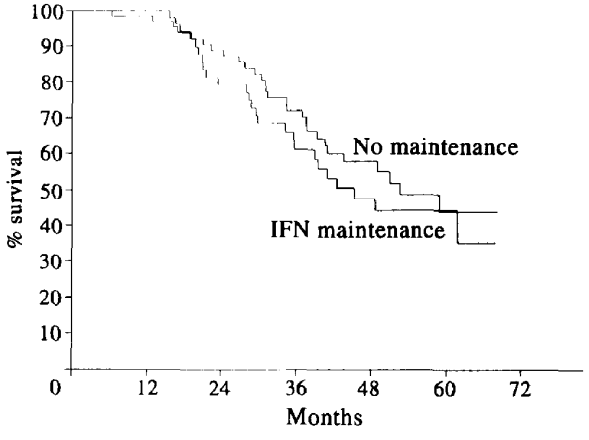

Figure 6. Survival (TRS) of MM patients randomised for IFNα maintenance (n = 52) or no maintenance treatment (n = 65) (n.s.).

MP therapy in stage I patients, a median delay from diagnosis to start of therapy of 12 months was reported [17]. Notably these authors could not show a survival advantage for initially treated stage I patients compared with those in which induction treatment was deferred [18]. Based on these results and our prospective observations, we conclude that the asymptomatic stage I and stage II patients of our trial would not have profited from early chemotherapy. Although the analysis of our patients' characteristics showed that plasma cell morphology and LI are two parameters with predictive impact, helping to identify non-progressive MM, a simple discriminating risk factor to be applied to single patients is still lacking. Therefore, a close follow up is needed to detect disease progression at an early stage, in order to determine the correct time point for commencing chemotherapy.

In a phase I/II trial, VBAMDex polychemotherapy produced high response rates in both untreated and pretreated MM patients [3]. Hence, we tested this combination prospectively comparing it with MP in high risk MM (stage III). We used VBAMDex regularly as second line therapy in primary or secondary MP resistant patients. We hoped to determine whether polychemotherapy schemes such as VBAMDex should be given as first line, or kept for second line treatment. Despite a higher response rate in the polychemotherapy group, together with a somewhat higher toxicity a survival advantage was not apparent for the VBAMDex treated group. Similar results have been obtained in many other trials testing MP versus polychemotherapy [2]. A compartment of chemotherapy resistant tumour cells, already existing at diagnosis, and which cannot be influenced by presently available chemotherapy but determines the survival of the individual patient, may explain this discouraging experience. Considering the additional fact that the extent of TCM reduction bears no relation to survival [13, 19], the conclusion has to be that further variants of currently available chemotherapy will probably not provide a major advance in future MM treatment. Rather, efforts to introduce alternative treatment strategies, for example the application of cytokines for controlling tumour growth, will have to be considered.

IFNα could be a useful tool in this context, since IFNα application in MM has produced response rates of approximately 20%, both in previously untreated as well as in chemotherapy resistant patients [5]. We therefore tested IFNα as maintenance after induction chemotherapy. However, neither remission duration nor survival were positively influenced. Similar results have been obtained in a large SWOG study [20], and an extended progression free period, but again no prolongation of survival has been reported in three other trials [21–23]. Since Österborg and colleagues did observe a survival advantage for IgA and Bence Jones MM patients treated with natural IFNα [24], we also analysed corresponding subgroups in our trial, but were unable to detect any benefit from IFNα maintenance treatment. However, the small number of patients in these subgroups does not permit any definite conclusions. A meta-analysis of patients' data from all relevant trials should be performed to investigate whether a subgroup of MM patients may be defined which profits from concomitant, or maintenance IFNα treatment.

Overall the results of this trial as well as of many others indicate that decisive advances of MM treatment will have to be based on a better understanding of the chain of molecular biological events leading to unrestricted proliferation of B lymphocyte clones resulting in MGUS, smoldering, or progressive multiple myeloma.

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