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ORIGINAL ARTICLE

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Retrolective cohort study of an additive therapy with an oral enzyme preparation in patients with multiple myeloma

Abstract *Purpose*: To evaluate the impact of an additive therapy with an oral enzyme (OE) preparation given for more than 6 months additionally to standard combination chemotherapy (vincristine/melphalan/cyclophosphamide/prednisone (VMCP)- or methylprednisolone/vincristine/CCNU/cyclophosphamide/melphalan (MOCCA)-regimen) in the primary treatment of patients with multiple myeloma stages I–III. *Methods*: A cohort of 265 patients with multiple myeloma stages I–III was consecutively treated at our institution in two parallel groups (control group ($n = 99$): chemotherapy ± OE for less than 6 months; OE-group ($n = 166$): chemotherapy + OE for more than 6 months). The median follow-up time in the stages I, II, and III for the OE-group was 61, 37, and 46.5 months, respectively; for the control group the respective values were 33, 51.5, and 31.5 months. The primary endpoint of the study was disease-specific survival. Secondary endpoints were response to therapy, duration of first response and side effects. The chosen method for evaluation was the technique of a retrolective cohort analysis with a concurrent control group. Survival analysis was performed by the Kaplan-Meier method and multivariate analysis was done with the Cox proportional hazards model. *Results*: Significantly higher overall response rates and longer duration of remissions were observed in the OE-group. Primary responders showed a longer mean survival time than non-responders. Additive therapy with OE given for more than 6 months decreased the hazard of death for patients at all stages of disease by approximately 60%. Observation time was not long enough to estimate the median survival for patients at stages I and II; for stage III patients it was 47 months in the control group versus 83 months for the patients treated with OE ($P = 0.0014$) which means a 3-year gain of survival time. Significant prognostic factors for survival, in the Cox regression analysis, were stage of disease and therapy with OE. The OE-therapy was generally well tolerated (3.6% of patients with mild to moderate gastrointestinal symptoms). *Conclusion*: OEs represent a promising new additive therapy in multiple myeloma which will be further evaluated in a randomized phase III trial in the USA.

Key words Retrolective cohort study · Additive treatment · Multiple myeloma · Oral enzyme preparation · Survival

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Introduction

Multiple myeloma is an incurable haematological disease characterized by the malignant transformation of a B-lymphocyte clone with terminal differentiation of the tumour cells into immunoglobulin-producing plasma cells which accumulate in the bone marrow. With an annual incidence of 2–4 per 100,000 people it accounts for 1% of all cancers and 14% of all haematological malignancies. Although myeloma is initially chemoresponsive, and many patients achieve clinical remission, median survival is only 36 months for patients with the advanced stage III. Even after high-dose chemotherapy and autologous transplantation, resistant cells of the malignant clone persist, and almost all patients eventually progress.

Survival of patients can be predicted by different prognostic factors (serum β_2-microglobulin, plasma cell

labelling index, C-reactive protein, serum creatinine, age), by stage of the disease and also by the mode of treatment. Since the 1960s the standard conventional treatment has consisted of melphalan and prednisone, resulting in a 40–50% response rate. Combinations of alkylating agents yield higher response rates, but no prolongation of median survival could be shown in various randomized trials [1–3]. Interferon maintenance usually prolongs response duration but in most studies does not significantly influence survival [4]. The use of bisphosphonates in patients with bone lesions, however, reduced bone complications and prolonged remission and even survival in a subgroup of patients [5].

At our institution we use as primary cytoreductive therapy the vincristine/melphalan/cyclophosphamide/prednisone (VMCP)-protocol [1, 6] in stages IB, IIA and B, the methylprednisolone/vincristine/CCNU/cyclophosphamide/melphalan (MOCCA)-regimen [7, 8] in stages IIB, IIIA and B. Therapy is given until response (remission or stable disease), or continuously (a maximum of five cycles in 1 year, with intervals of 4–8 weeks between cycles depending on the full recovery of haematological parameters after each cycle). Since the oral enzyme (OE) preparation was available to us in 1989, some of our patients were treated in addition to chemotherapy, with this fixed combination product containing the plant proteinase papain and the proteases trypsin and chymotrypsin.

The mechanism of action of enzymes is not fully understood but there is a variety of effects which are thought to contribute to their clinical efficacy: By irreversible binding of these orally applied proteases to antiproteinases such as α_2-macroglobulin and α_1-antitrypsin, synthesis of these antiproteinases is induced. Elevated levels of antiproteinases inactivate other proteinases such as cathepsins, which are thought to play a role in tumour development and in metastasis. For cystein proteinases of plant origin (papain) an influence on the balance between proteinase and antiproteinase may also influence tumour metastasis [9, 10]. Furthermore, enzymes are known to interact with the cytokine network: the binding of proteinases to α_2-macroglobulins leads to α_2-macroglobulin-proteinase complexes with a high capacity for binding and clearing cytokines like IL-1β, IL-6 (a known promoter of multiple myeloma), TNF-α, IFN-γ, and TGF-β. TGF-β promotes immunosuppression in the host, and tumour immune escape, thus modulating tumour growth [11]; enzymes reduce TGF-β overproduction at mRNA and protein levels [12, 13]. Enzymes also interact with adhesion molecules which play an important role in tumour development and metastasis. The modulation or down-regulation of adhesion molecules by enzymes was shown amongst others for B7-1, CD4, CD29, CD44, CD49, CD51, CD54, CD58, which may contribute to their anti-tumour efficacy [10]. In patients with multiple myeloma, a significant reduction in CD29, CD54, and CD58 could be found after the oral intake of enzymes, which correlated well with the clinical benefit in these patients [14]. Finally, enzymes influence the antioxidant enzyme level and reactive oxygen molecules. An increase in the synthesis of anti-oxidative protective mechanisms by exhibiting a small chronic oxidative stress was shown in patients with burn injuries [15, 16]. Recently, a novel role for extracellular proteases as inhibitors of intracellular signal transduction pathways was described [17].

In subgroups of our patients we have analyzed the effects of OE not only on the clinical parameters of efficacy such as remission/response, duration of remission/response, and long-term outcome, but also on the correlation of efficacy with progression markers of the disease. We observed that serum concentrations of the soluble TNF receptors sTNF-R p55, sTNF-R p75, and β_2-microglobulin increased with the progression of multiple myeloma stages II and III before treatment. Chemotherapy, and to a greater extent chemotherapy with additional application of OE, decreased the concentrations of these molecules [18]. The same holds true for TGF-β. In addition we observed a clear correlation between the concentration of immunoreactive IL-6 and the severity of the disease [12, 19].

The intention of the study presented here is to analyze the data of all patients treated with OE for longer than 6 months in addition to chemotherapy, in order to substantiate our earlier results concerning therapeutic efficacy and safety. Reference is a group of patients treated at the same time with standard chemotherapy only or with a short-term enzyme therapy (<6 months). The method chosen is the technique of a retrolective cohort analysis with a concurrent control group which allows valid conclusions on therapeutic efficacy and tolerability of a treatment if certain prerequisites are fulfilled. In this connection a special emphasis is given to the pre-specified study protocol containing study design, selection rules for centres, eligibility criteria for patients, definition of principal endpoints along with the assessment of the clinical relevance of observed changes, definition of treatment groups, statistical methods, test hypotheses, and data quality assessment [20].

Patients and methods

Study patients

From January 1987 to July 1997, 333 patients with multiple myeloma were diagnosed at the Clinic for Haematology and Transfusion Medicine of the University of Bratislava, and were eventually treated and followed-up. Diagnosis and staging was done according to Durie and Salmon taking into account the type of myeloma (secretory or non-secretory) and the substages A and B (A with normal, B with pathological renal findings defined by elevated serum creatine levels). Patients were characterized by age, gender, body height and weight on admission, occupation, risk factors for comorbidity (malignancies in the family, smoking, alcohol and/or drug abuse, etc.), risk factors of the disease (β_2-microglobulin, stage of the disease, secretory myeloma, osteolysis, infections) and by myeloma-specific laboratory parameters. All patients fulfilling the inclusion criteria (primary diagnosis of

multiple myeloma stages I-III/A and B, age 18–80 years, treatment with chemotherapy), and for whom the exclusion criteria (adjuvant therapy with other enzyme preparations, adjuvant immunotherapy with other products, presence of a second carcinoma or another malignoma on admission) did not apply, were included in the data analysis.

Treatment and follow-up

Chemotherapy: stage IB, IIA and B patients were given the VMPC-regimen, consisting of vincristine 1 mg i.v. day 1, melphalan 6 mg/m^2 p.o. days 1 + 4, cyclophosphamide 125 mg/m^2 p.o. days 1–4, prednisone 60 mg p.o. days 1–4. Stage IIB, IIIA and B patients were administered the MOCCA-regimen: methylprednisolone 0,8 mg/kg i.m. days 1–7, 0.4 mg/kg i.m. days 8–14, vincristine 0.03 mg/kg i.v. day 1, CCNU 40–80 mg p.o. day 1, cyclophosphamide 10 mg/kg i.v. day 1, melphalan 0.25 mg/kg p.o. days 1 + 5. In chemotherapy-resistant cases or after relapse the vincristine/adriamycin/dexamethasone (VAD) scheme [21] was applied (vincristine 0.4 mg/day continuously i.v. days 1–4, adriamycin 9 mg/m^2/day continuously i.v. days 1–4, dexamethasone 40 mg/day p.o. days 1–4, 17–20. Chemotherapy was started at time of diagnosis and given until response (remission or stable disease), or continuously (a maximum of five cycles in 1 year, with intervals of 4–8 weeks between cycles depending on the full recovery of haematological parameters after each cycle). Patients remained under close observation, and reinduction chemotherapy was started in case of clinical or laboratory progression (increase of ESR, paraprotein, etc.). In stage IIA all patients with osteolytic or osteoporotic bone changes received bisphosphonates (clodronic acid, 400 mg b.i.d.), calcium and vitamin D additionally.

OE (Wobe-Mugos E, MUCOS Pharma, Geretsried, Germany; gastric juice-resistant coated tablets consisting of 100 mg papain, 40 mg trypsin, 40 mg chymotrypsin) were given orally as two tablets t.i.d. for the first year, starting at day 1 of chemotherapy. Treatment allocation to OE or "no-OE" was decided individually by the responsible physician by chance only depending on the availability of OE on the first day of chemotherapy of the particular patient. The dose was usually reduced to one tablet t.i.d. from the second year on, and continued throughout the full observation period.

For evaluation of response standard SWOG criteria were used [2, 22, 23]. Complete remission was defined as a more than 75% decrease of paraprotein and/or >90% decrease of proteinuria respectively, decrease of plasma cells in the bone marrow under 5%, normal values of β_2-microglobulin and kidney function, and improvement of clinical parameters (weakness, bone pain, no new osteolytic foci). Partial remission was characterized as clinical improvement, and reduction of plasmocytosis in bone marrow, with regression of paraprotein in serum by 50–75%. Stable disease was characterized as clinical improvement with regression of paraprotein by 25–50%.

Statistical methods/data collection

The study type chosen for this analysis was a controlled, unicentric, longitudinal, retrolective cohort study design with forward data collection in two parallel groups [20]. Patients qualified as enzyme-patients if treatment with OE had been for longer than 6 months. Patients who had received enzyme therapy for less than 6 months were not excluded but were included in the analysis as "not enzyme-treated". Intent-to-treat analyses including all patients receiving at least once OE were also performed. The primary endpoint of the study was disease-specific survival calculated from the day of first diagnosis. Secondary endpoints were response to therapy (response quality and rate) during the first year of therapy, duration of first response and side effects of the therapy. All data were transferred to standardized case-report forms which were collected by an external institution (IFAG, Basle), checked for completeness and plausibility, and monitored (data audit). Estimation of the cumulative distribution of disease-specific survival was calculated according to the Kaplan-Meier method. Multivariate analysis of the data was performed with the Cox proportional hazards model with fixed covariates without inclusion of interaction terms. All P values were 2-sided, with hazard- or odds ratios and 95% confidence intervals.

Results

Patients

In the 333 patients admitted from January 1987 to July 1997, disease stage I was diagnosed in 75 patients, stage II in 160 patients, and stage III in 98 patients. Patients not receiving treatment (chemotherapy or chemotherapy with additional OE; $n = 39$) or patients receiving only OE ($n = 29$) were excluded from the evaluation. Thus, of the 333 patients with multiple myeloma diagnosed, treated and followed-up, 265 were eligible for this analysis. As defined in the test plan, 14 patients having received additive OE for less than 6 months (observation time <6 months) were assigned to the control group but were also analyzed in an intent-to-treat analysis in the enzyme group. The total evaluable sample consisted of the OE-group ($n = 166$) and the control group ($n = 99$) (Table 1). Treatment groups were well matched for age, gender, risk factors in their medical history (data not shown), risk factors of the disease, and laboratory parameters. However, statistically significant differences were observed for age in the total sample adjusted for disease-stage (but the median age-difference of 4 years was regarded as clinically irrelevant), CRP (OE-group < control group) and haemoglobin (OE-group >control group) in stage I patients and β_2-microglobulin (OE-group < control group) in stage II patients. Seventy-four percent of the patients in both groups had a secretory multiple myeloma; osteolytic and other bone changes were manifest in 71% of the cases, recurrent infections in 15% (Table 2).

The median follow-up time calculated from the study beginning to the study end or death of the individual patients was 40.8 months in the OE-group and 39.5 months in the control group, while the median

Table 1 Patients treated in the institution and their attribution to the groups for statistical analysis (*OE* oral enzymes)

Multiple myeloma patients	Number	%
Patient-data collected	333	100
Therapy		
No therapy	39	11.7
OE only	29	8.7
Chemotherapy ± OE	265	79.6
Patients analyzed	265	100
Per protocol (OE > 6 months)		
Chemotherapy + OE	166	62.6
Chemotherapy	99	37.4
Intent-to-treat (OE >0 months)		
Chemotherapy + OE	180	67.9
Chemotherapy	85	32.1

Table 2 Patients' characteristics at baseline (all stages, per-protocol sample) (*SD* standard deviation)

	OE-group	Control group	*P* Value
Age (years) mean (SD)	62.45 (11.30)	66.17 (10.95)	0.009[a]
Gender (*n*): male/female (%)	79 (47.6)/87 (52.4)	50 (50.5)/49 (49.5)	0.646[b]
Body weight (kg) mean (SD)	74.13 (13.66)	72.25 (10.96)	0.277[a]
Stage (Durie & Salmon) *n* (%)			
I	19 (11.4)	11 (11.1)	
II	93 (56.0)	52 (52.5)	0.813[b]
III	54 (32.5)	36 (36.4)	
Myeloma type			
Secretory	121 (73.3)	73 (74.5)	
Nonsecretory (micromolecular)	4 (2.4)	3 (3.1)	0.538[b]
Other (diffuse, latent)	5 (3.0)	0	
Paraproteins present *n* (%)	124 (76.5)	71 (73.2)	0.609[b]
Osteolysis, osteoporosis, fractures *n* (%)	105 (70.5)	58 (70.7)	0.667[b]
Bone pain present *n* (%)	113 (72.0)	68 (71.6)	0.250[b]
Recurrent infections *n* (%)	22 (13.7)	18 (18.6)	0.293[b]
Karnofsky index mean (SD)	80.67 (9.60)	76.39 (11.50)	0.002[a]
Laboratory values (mean (SD)			
Thrombocytes 1,000/ul	225.6 (103.6)	229.3 (78.5)	0.768[a]
Hemoglobin (g/dl)	12.3 (1.89)	11.8 (2.0)	0.053[a]
CRP mg/l	19.9 (29.2)	26.0 (31.3)	0.376[a]
BSR mm/1h	58.1 (42.9)	71.0 (42.8)	0.023[a]
Total protein g/l	80.6 (15,7)	81.2 (18.5)	0.767[a]
IgA g/l	5.44 (10.19)	4.92 (9.33)	0.695[a]
IgG g/l	26.7 (25.8)	28.5 (24.1)	0.589[a]
IgM g/l	2.89 (12.97)	1.22 (1.24)	0.227[a]
β_2-microglobulin (mg/l)	4.22 (4.18)	5.07 (3.89)	0.263[a]
BM-plasma cells (%)	19.6 (18.6)	25.1 (20.3)	0.038[a]

[a] Two-sided *t*-test
[b] χ^2-test (Pearson)

Table 3 Frequency of distribution of chemotherapy regimens and sequences (*OE* oral enzyme, *VMCP* vincristine/melphalan/cyclophosphamide/prednisone, *MOCCA* methylprednisolone/vincristine/CCNU/cyclophosphamide/melphalan, *VAD* vincristine/adriamycin/dexamethasone)

Regimen *n* (%)	OE-group	Control group	*P* value
VMCP	38 (22.9)	35 (35.4)	
MOCCA	53 (31.9)	33 (33.3)	
VAD	0	1 (1.0)	
VMCP/VAD	1 (0.6)	0	0.120[a]
MOCCA/VAD	9 (5.4)	2 (2.0)	
MOCCA/VMCP	57 (34.3)	26 (26.3)	
All three combined	8 (4.8)	2 (2.0)	

[a] χ2-Test (Pearson)

treatment duration in the OE-group was 24.2 (mean = 33.9) months. The median follow-up time by disease stage in the OE-group was 61 months, 37 months, and 46.5 months for stages I, II, and III, respectively. For the control group the respective values were 33 months (I), 51.5 months (II), and 31.5 months (III). The frequency of distribution of the individual chemotherapy regimens is given in Table 3. In the OE-group in the cases of multiple myeloma stage III ($P = 0.011$) and in the stage-adjusted total sample ($P = 0.0086$), sequential polychemotherapy combinations were used significantly more frequently than in the control group. This can only partly be explained by longer observation times. A possible influence on survival was analyzed and accounted for by an adjustment in the Cox proportional hazard regression model, where the covariate "type of chemotherapy" had no significant, independent influence on the survival time function.

Response

In the OE-group the proportion of patients achieving complete remission, partial remission or stable disease after first-line chemotherapy ("responders") was significantly higher than in the control group (97.6% vs. 69.7%) in all stages ($P = 0.001$). In stage III there were only 3.7% non-responders in the OE-group but 38.9% in the control group ($P < 0.001$) (Table 4). The duration of the first remission or stable disease was significantly longer in the OE- than in the control group in stages II and III, the average in stage III being 37.3 vs. 11.6 months.

Survival

During a median observational period of 41 months, a total number of 28 (28.3%) disease-related deaths were recorded in the control group: 18 in stage III, 9 in stage II, and 1 in stage I. In the OE-group (OE given for more than 6 months) the total number of events was 27 (16.3%) during a median observational period of 40 months with 21 in stage III, and 6 in stage II. The Kaplan-Meier univariate analysis with logrank-test showed that the median disease-specific survival time in stage III was 47 months (95% CI: 32–62 months) in the control group versus 83 months (95% CI:

Table 4 Response to treatment; frequency and type of first response (*OE* oral enzyme, *CR* complete remission, *PR* partial remission, *SD* stable disease, *NR* no response)

Response	Stage I		Stage II		Stage III	
	OE-group *n* (%)	Control group *n* (%)	OE-group *n* (%)	Control group *n* (%)	OE-group *n* (%)	Control group *n* (%)
CR	0	2 (18.2)	3 (3.2)	0	0	0
PR	7 (36.8)	1 (9.1)	27 (29.0)	6 (11.5)	16 (29.6)	4 (11.1)
SD	12 (63.2)	2 (18.2)	61 (65.6)	36 (69.2)	36 (66.7)	18 (50.0)
NR	0	6 (54.5)	2 (2.2)	10 (19.2)	2 (3.7)	14 (38.9)
Responder (CR + PR + SD)	19 (100)	5 (45,5)	91 (97,8)	42 (80,8)	52 (96,3)	22 (61.1)
P [a]	$P = 0.001$	$P = 0.001$	$P = < 0.001$			

[a] Fisher exact test

Table 5 Disease-specific survival according to the stages in the intent-to-treat and per-protocol analysis (*OE* oral enzyme, *MM* multiple myeloma)

	OE-group				Control group				
	n	Deaths related to MM	Median survival (months)	95% CI	*n*	Deaths related to MM	Median survival (months)	95% CI	*P* (Logrank)
OE > 0 Months (intent-to treat)									
Stages I–III	181	31	–	–	84	24	–	–	0.0051
Stage I	20	0	–	–	10	1	–	–	0.1573
Stage II	98	6	–	–	47	9	–	–	0.1217
Stage III	63	25	83	55–112	27	14	49	44–55	0.0342
OE >6 Months (per protocol)									
Stages I–III	166	27	–	–	99	28	–	–	0.0003
Stage I	19	0	–	–	11	1	–	–	0.1888
Stage II	93	6	–	–	52	9	–	–	0.1493
Stage III	54	21	83	50–117	36	18	47	32–62	0.0014

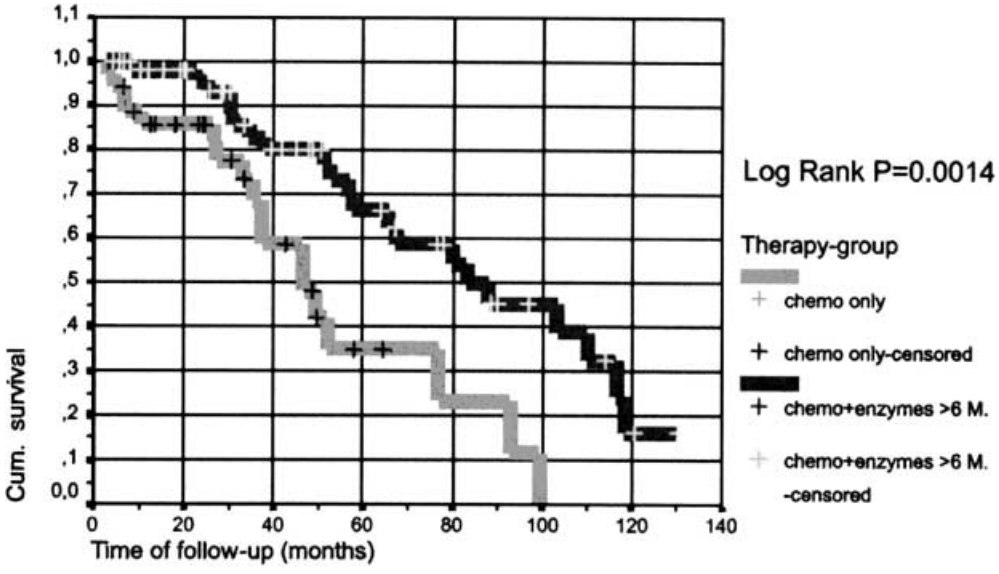

Fig. 1 Kaplan-Meier estimate of survival and logrank test (logrank $P = 0.0014$) of patients in stage III

50–117 months) in the OE-group ($P = 0.0014$), corresponding to a 3-year gain in survival time (Table 5; Fig. 1). Because of the small number of events in stages I and II, in these subgroups the median survival time could not be estimated. However, in a global analysis of myeloma stages I to III, a highly significant prolongation of survival time could be found (stage-adjusted result: $P = 0.0003$; Fig. 2). Mean survival time was shown to be dependent on the initial response to the therapy. From the survival analysis with censored data (Kaplan-Meier estimate with logrank-test) the mean survival time in the primary responders was 130 months and in the primary

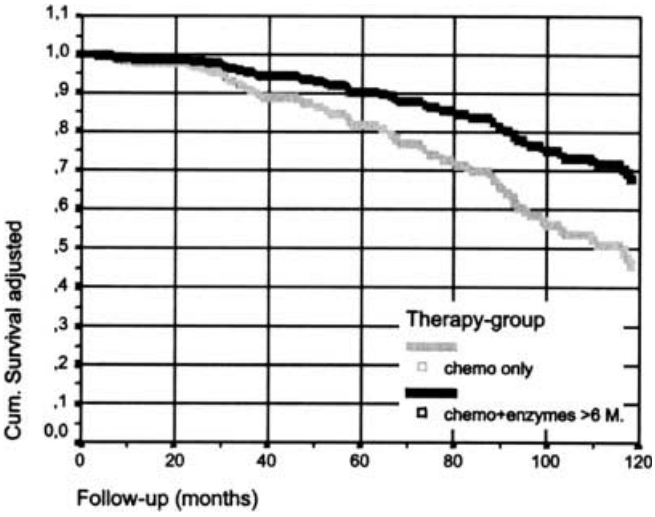

Fig. 2 Cox regression analysis of survival of patients (all stages), adjusted for demographic and risk confounders. *P* (therapy) = 0.0288, OR = 0.496 (95%CI = 0.27–0.93)

non-responders 51 (median = 47) months with 19.2% vs. 29.4% myeloma mortality ($P = 0.0000$).

An "intent-to-treat" analysis assigning all patients having ever received enzymes into the OE-group ($n = 181$) – even if the enzyme therapy was discontinued early or lasted only for a short period (< 6 months) – did confirm the above result (Table 5). Regarding the impact of the initial chemotherapy regimen on survival in stage III, similar median survival times were found for the control group (VMCP: 47 months; combinations: 49 months; MOCCA: 52 months) which could be improved by the addition of OE (VMCP + OE: 57 months; MOCCA + OE: 88 months, $P = 0.0093$; combinations + OE: 103 months $P = 0.0027$). Finally the analysis of the substages showed that a considerable prolongation of the median survival time by 29 months could also be achieved in the myeloma stage III B.

Concerning overall mortality (including non-myeloma-related deaths) the median survival time advantage in the OE-group was 33 months in stage III ($P = 0.0059$) and was also significant in the stage-adjusted total sample ($P = 0.0039$).

Multivariate analysis: to examine for possible confounding influences on the observed treatment effects, the Cox proportional hazard model was used to regress survival on a number of other possible confounders such as stage, age, gender, myeloma type, myeloma substage, and chemotherapy regimen, besides the dummy variable for the two treatment groups. Relevant prognostic factor for survival was the stage of disease. Of the 265 study patients, 257 could be evaluated multivariately, and the estimated value of the stage-related, independent hazard of death increased by more than six-fold with the disease stage. The additive therapy with OE in all stages combined led to an estimated reduction of the hazard of death by approximately 60% ($P = 0.0011$; Table 6, Fig. 2). Age, gender, myeloma type, myeloma substage, type of chemotherapy, Karnofsky index and percentage of bone marrow plasma cells had no significant, independent influence on survival in this analysis.

Table 6 Multivariate analysis of disease-specific survival. $n = 257$, 67 myeloma-related deaths, all 3 stages combined, Cox regression model

Covariate	*P* value (Wald)	Hazard ratio (95% CI)
Stages I–III	0.0000	6.2371 (3.4932–11.136)
Therapy with/without OE	0.0011	0.3965 (0.2276–0.6907)
Age	0.8502 (n.s.)	0.9975 (0.9716–1.0240)
Gender	0.8341 (n.s.)	1.0592 (0.6185–1.8138)
Type of myeloma (secretory/non-secretory)	0.5331 (n.s.)	0.8014 (0.3994–1.6079)

Safety

On the whole, relatively few-side effects were documented. According to the physician's documentation six side-effects were associated with OE-therapy, while 28 were related to chemotherapy. All side-effects associated with OE were gastrointestinal disorders (meteorism: $n = 2$, diarrhoea: $n = 1$, nausea: $n = 1$, others: $n = 2$) graded as mild to moderate. In five cases the side effects were of transient nature, and in one case it did not completely normalize. There were no serious side effects associated with OE, nor was there a therapy discontinuation due to intolerance. OE therapy as an additional treatment in multiple myeloma was therefore regarded as safe in terms of adverse events. The side-effects of chemotherapy were mainly leukopenia ($n = 24$), thrombocytopenia ($n = 2$) and anaemia ($n = 2$); their severity was graded in 13 cases as mild, in 15 cases as moderate.

Discussion

Principal changes have occurred in multiple myeloma treatment in the course of the recent years. Even if "classics" still recommend standard treatment with melphalan and prednisone, the concomitantly observed survival time of only 3–4 years is disappointing. Presently, many hints exist that combined chemotherapy is more effective in induction of remissions, and may lead to a prolongation of median survival to more than 5 years especially if combined with radiotherapy, immunotherapy, and osteoprotective and other supportive treatment. Intensive treatment of multiple myeloma with high-dose melphalan (100–200 mg/m^2) in combination with autologous or allogeneic bone-marrow transplantation or peripheral blood stem cell transplantation enhances the complete remission rate to 30%, can prolong duration of remission and even median survival to more than 5 years and is therefore recommended for younger patients (< 60–65 years) [24, 25]. Because of high morbidity and mortality in the first year (up to 50%) allotransplantation in multiple myeloma cannot be rec-

ommended outside clinical studies. The most serious problem is that years after intensive treatment and transplantation, many patients relapse and need salvage chemotherapy. For effective prolongation of survival a combination of chemotherapy with immunomodulatory or complex supportive therapeutic modalities will be necessary. The beneficial influence of enzyme therapy was suggested by the observation of a decrease of sTNF, IL-6, β_2-microglobulin and paraprotein levels [12]. According to our clinical experience with multiple myeloma treatment and the present statistical analysis, the addition of enzymes substantially improves the clinical status and overall survival. The mechanism of action of enzymes is not fully understood yet. Oral enzyme combinations containing papain, trypsin and chymotrypsin influence the cytokine network and adhesion molecules (integrins, immunoglobulin superfamily and many other membrane receptors, according to various studies). They contribute to antitumour and antimetastatic efficacy (reduction of CD44 hyaluronate "homing" receptor) [9, 10, 12–14, 26]. Similar results were found in our patients: After oral intake of enzymes by patients, we observed after 24 hours a significant reduction of CD29−, CD38−, CD44−, CD54− and CD58− density on peripheral lymphocytes. Binding of proteinases to α_2-macroglobulin complex may reduce cytokine levels (TNFα, TGF-β, IL-1, IL-6, IFN) in the plasma of patients with malignancies. We think that OE therapy in combination with cytostatic chemotherapy opens new possibilities of treatment strategies for multiple myeloma. These promising results will be further evaluated in a prospective randomized phase-III study which is currently running in the USA and Canada under an orphan drug designation.

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