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Induction and Maintenance Therapy in Multiple Myeloma: a Multicenter Trial of MP versus VCMP

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Abstract—*In a prospective multicenter trial, 320 untreated myeloma patients of stage II and III were randomized for remission induction into two groups receiving six monthly courses of either MP or VCMP treatment. Response rates were equal in both groups: 72% remission, 21% no change, 7% progress for patients evaluable by TCM changes and 56% remission, 11% no change, 33% progress for BJ- and non-secretory myelomas. The overall survival rate was 60% after 4 years. An unexpected finding was the significantly longer survival of MP treated patients compared to the VCMP group. After successful remission induction, patients were randomized into one group receiving maintenance treatment using the induction scheme q 8 weeks, and another group without further chemotherapy. Although patients in the latter group relapsed significantly earlier, differences between both groups concerning acquired resistance to first line therapy or survival have not been noticed to date.*

INTRODUCTION

MULTIPLE MYELOMA (MM) is a disseminated tumor of B-lymphocyte origin. At the time of diagnosis, patients usually present with a large tumor burden. The prognosis for myeloma patients has clearly improved since the introduction of chemotherapy, and a median survival of between 24 and 36 months has been reported [1–3]. With the exception of a few cases showing long term complete remissions after ultraaggressive melphalan treatment [4], curative treatment is not available at present. The combination of melphalan and prednisone (MP) has been known for many years as an effective chemotherapy with little toxicity [5, 6]. A large number of different drug combinations have been compared with MP in prospective trials; while a few of these have been shown to induce better remission rates, prolongation of survival has not been demonstrated beyond doubt [2, 3, 6–16].

The four-drug combination VCMP with low toxicity has been brought forward as one alternative for first line therapy of MM [17]. We have planned a prospective randomized trial comparing MP and VCMP for both induction and maintenance therapy in 1982, since long term observations concerning VCMP were not available at that time, particularly regarding the efficacy of this drug combination for maintenance treatment.

The tumor cell mass (TCM) calculation described by Salmon and Wampler [18] has been proposed for initial staging and follow-up of MM patients [19]. Testing the usefulness of this method for monitoring treatment results in a controlled

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multicenter study has been another goal of this trial.

Three groups have so far investigated the value of maintenance chemotherapy after remission induction in MM [20–22]. A survival advantage of patients on maintenance therapy has not been demonstrated in any of these studies, although higher relapse rates in unmaintained patients have been observed. We have examined this question once more reaching results similar to those reported before.

The present paper describes the results of a four year prospective study conducted by the German Myeloma Treatment Group.

MATERIALS AND METHODS

Patients

Between 1982 and 1986, 320 untreated patients with multiple myeloma of stage II and III [19] entered the study and were randomized for either MP or VCMP induction chemotherapy. The patients' characteristics are summarized in Table 1. Twenty-one hospitals in the Federal Republic of Germany participated in the study: five of them took care of more than half of the patients (173/320). There were no significant differences in patients' characteristics between these five hospitals, or between this group and 147 patients from the remaining institutions. Sixty-two patients had to be excluded from the study before completion of the induction phase because of protocol violation, refusal to comply, loss to follow-up or incomplete documentation. At present the median observation time of all patients amounts to 550 days in both treatment groups.

Staging and follow-up

The method described by Durie and Salmon [19] based on tumor cell mass (TCM) calculation was used for initial staging. Treatment responses were estimated by changes of the individual TCM as determined by the changes of the serum myeloma protein concentration [18]. A TCM reduction between 25% and 75% was defined as minor remission, a reduction of more than 75% was called major remission, an increase of the TCM by more than 25% above the initial value was defined as progress, and a relapse was stated if a >25% increase of the TCM occurred after successful remission induction. Minor variations (± 25%) of the TCM were designated as a no change result. Additionally in all patients and particularly in Bence Jones and nonsecretory myelomas, the response was estimated by clinical parameters, i.e. enlargement of bone lesions, changes in bone marrow infiltration, appearance or disappearance of hypercalcemia, and the Karnofsky performance status.

Table 1. Registered MM patients characteristics before treatment

Characteristics	MP group *n* (% of MP)	VCMP group *n* (% of VCMP)	Total *n* (% of total)
All patients	170	150	320 (100)
Median age (years)	62	62	62
Stage II	77 (46)	76 (51)	153 (48)
Stage III	92 (54)	74 (49)	166 (52)
Mean TCM ($\times 10^{12}$ cells/m^2 body surface area)	1.22	1.30	1.26
Patients with serum myeloma protein			
IgG	107 (63)	84 (56)	191 (61)
IgA	35 (21)	38 (25)	73 (23)
IgD	0 (0)	0 (0)	0 (0)
IgE	4 (2)	1 (1)	5 (2)
Patients with Bence Jones protein in the urine			
kappa	56 (33)	51 (34)	107 (35)
lambda	29 (17)	44 (29)	73 (23)
Bone lesions			
no	6 (4)	14 (9)	20 (6)
osteoporosis	31 (18)	21 (14)	52 (16)
1–3 lytic lesions	34 (20)	39 (26)	73 (23)
> 3 lytic lesions	99 (58)	76 (51)	175 (55)
Bone marrow infiltration by more than 20% plasma cells	129 (76)	118 (79)	247 (79)
Serum hemoglobin < 8.5 g/dl	18 (11)	23 (15)	41 (13)
Serum calcium > 3.0 mmol/l	16 (9)	18 (12)	34 (11)

Chemotherapy schedules

MP: melphalan 8 mg/m^2 p.o. days 1–4; prednisone 60 mg/m^2 p.o. days 1–4; q 4 weeks.

VCMP: vincristine 1 mg i.v. day 1; cyclophosphamide 100 mg/m^2 p.o. days 1–4; melphalan 5 mg/m^2 p.o. days 1–4; prednisone 60 mg/m^2 p.o. days 1–4; q 4 weeks.

Design of the trial

Untreated myeloma patients (stage II and III) were staged and randomized for the MP or VCMP treatment group. After six successive therapy cycles, patients in remission were randomized once more into one group continuing with the chemotherapy of the induction phase q 8 weeks for maintenance, and another group receiving no maintenance therapy. Patients relapsing in the no maintenance group received reinduction therapy using the same schedule, which they had been given during the induction phase. Primarily resistant patients not responding to the induction therapy as well as those progressing under maintenance or while receiving reinduction treatment in the no maintenance group (secondary resistance), were treated with one of three salvage therapy regimes (etoposide, adriamycin/vindesine, or the five-drug combination VBAMDex) [23, 24].

RESULTS

MP versus VCMP

Of 320 patients who were randomized into MP and VCMP treatment groups, one half were classified as stage II, whereas the other half presented as stage III (Table 1). Two hundred and thirty patients were evaluated for the effect of induction chemotherapy. In 158 cases the efficacy could be judged on the basis of calculated TCM changes (Table 2). Seventy-two per cent of these patients remitted under chemotherapy; nearly half of them showed a major remission (> 75% reduction of the initial TCM), 7% progressed and 21% remained in a no change status. Differences between both treatment groups were not detected also after stratification in stage II or stage III patients (Table 3). Remitting patients with high initial TCM (stage III) achieved a major remission more often compared to stage II patients ($P < 0.01$). The mean TCM of all patients responding to the chemotherapy decreased from 1.3×10^{12} cells/m^2 (range $0.6–1.9 \times 10^{12}$) to 0.4×10^{12} cells/m^2 (range $0–1.4 \times 10^{12}$), i.e. by two thirds.

In 57 patients without measurable myeloma protein in their serum TCM changes could not be calculated. They were therefore judged by clinical, X-ray and other laboratory parameters (see Materials and Methods). Here remission could be induced in 56%, again without any differences between the MP and VCMP groups (Table 4).

In 15 patients the response by TCM calculation differed from the assessment by other response parameters (see Methods). In 12 patients the TCM calculations indicated a remission which was not confirmed by clinical judgement (Table 5); new

Table 2. Remission induction in MM patients evaluable by TCM changes

		TCM reduction > 75%	75–25%	No change	Progress
Total	% (n = 158)	33	39	21	7
MP group	% (n = 79)	33	39	20	8
VCMP group	% (n = 79)	33	38	22	7

Table 3. Remission induction in MM patients evaluable by TCM changes: stage II versus stage III

			TCM reduction > 75%	75–25%	No change	Progress
MP	II	% (n = 37)	24	52	16	8
group	III	% (n = 42)	40	29	24	7
VCMP	II	% (n = 42)	21	52	17	10
group	III	% (n = 37)	46	22	27	5

Table 4. Remission induction in MM patients not evaluable by TCM changes (Bence Jones or nonsecretory myeloma), assessed by clinical, laboratory and X-ray criteria

		Remission	No change	Progress
Total	% (n = 57)	56	11	33
MP group	% (n = 32)	53	13	34
VCMP group	% (n = 25)	60	8	32

Table 5. Remission induction evaluated by clinical, laboratory and X-ray criteria and compared to the TCM changes: n = 173

	Clinical remission	Clinical no remission
Remission evaluated by TCM	113	12
No remission evaluated by TCM	3	45

lytic bone lesions developed in five of them. In three patients a clinical remission was stated despite unchanged or progressing TCM. In all of these cases, further treatment decisions were made on the basis of clinical assessment.

The survival probability of all 320 patients that entered the study was 60% at 4 years after starting chemotherapy (Fig. 1). As expected, stage II patients survived better than stage III patients ($P < 0.008$). Surprisingly, the survival of MP treated patients exceeded that of the VCMP group ($P < 0.01$, Fig. 2) Twenty-two tumor related deaths were found in the MP and 37 in the VCMP group. Differences in initial TCM of these patients (MP: mean 1.36×10^{12}; VCMP: mean 1.29×10^{12}) or second line therapy could not be demonstrated. Ten MP versus five VCMP patients died during the induction phase ($P < 0.02$).

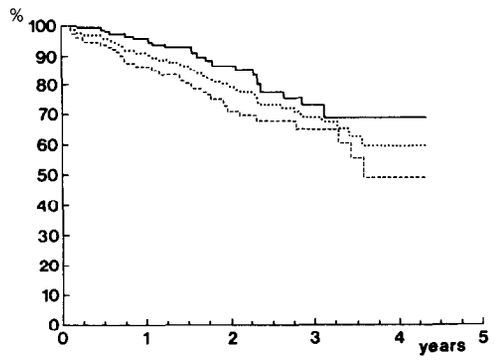

Fig. 1. Survival of all (...), stage II (—) or stage III (---) patients (stage II versus stage III: P < 0.008).

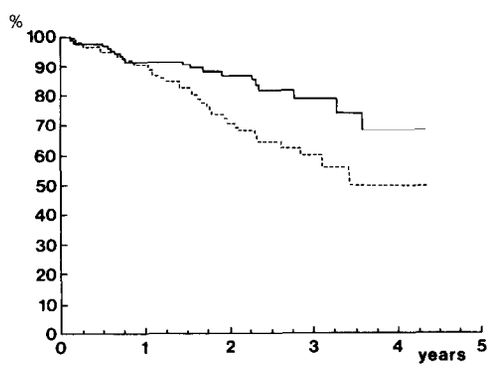

Fig. 2. Survival of MP (—) and VCMP (...) treated patients (P < 0.02).

Renal failure caused the death of two patients in the MP and of 12 in the VCMP group ($P < 0.05$). Lambda Bence Jones proteins were found slightly more often in the VCMP compared to the MP group of patients (29% versus 17%; Table 1), but occurred in a similar frequency in patients who died (33% in the VCMP versus 23% in the MP group). These data therefore do not support the notion that presence of a lambda Bence Jones protein constitutes a risk factor for tumor related death by renal failure.

Lethal toxicity during first line therapy occurred only three times (MP: 1; VCMP: 2). Twenty patients (MP: 12; VCMP: 8) had to be excluded from the study because of prolonged drug related toxicity, mostly of hematological type.

Homogeneity of the multicenter trial

Since five of the 21 participating hospitals cared for more than half of the patients (173/320), their results were evaluated separately and compared with those of the multicenter study. The number of patients at each hospital varied between 20 and 65 (mean 34.6). The response rates were similar to the main study, the overall survival ranged from 55% to 78% (mean 65%) after 4 years. Survival differences betwen the MP and VCMP groups were not detectable, because the number of patients at each hospital was too small for a statistical evaluation.

Maintenance versus no maintenance

After successful remission induction with either MP or VCMP, 123 patients were randomized into one group receiving no further chemotherapy and a second one continuing with either MP or VCMP cycles q 8 weeks. Relapses occurred significantly earlier in the no maintenance group (Fig. 3). Within 2 1/2 years after remission induction (i.e. 3 years after beginning of the initial chemotherapy) all patients in the no maintenance group experienced their first relapse, whereas in the maintenance group 75% of the patients were still in remission. However,

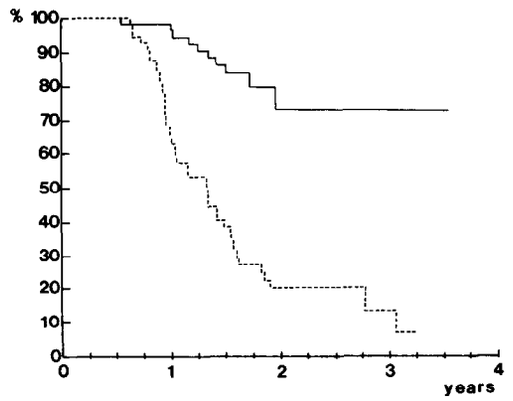

Fig. 3. First relapse after remission induction under maintenance (—) or no maintenance (...) therapy (P < 0.0001). *Time 0: start of initial chemotherapy.*

a high proportion of relapsing patients in the former group responded once more to their original chemotherapy, a survival advantage for the maintenance therapy group has not become apparent to date, i.e. 4 years after commencement of therapy (Fig. 4).

The probability of acquiring resistance to the first line therapy was identical in both groups and amounted to 20% of 2 years after commencing initial chemotherapy (Fig. 5).

Patients achieving a major remission initially relapsed earlier (50% at 12 months) than those with only minor remissions (50% at 27 months; $P < 0.004$).

DISCUSSION

Chemotherapy prolongs the survival of multiple myeloma patients significantly [1]. Although many alternative therapy protocols have been proposed, the intermittent treatment with melphalan and prednisone (MP), well tolerated by the patients, has remained the standard protocol for the last two decades [2, 3, 6]. In several prospective randomized studies, no other drug schedule has been found to consistently induce better survival rates, although significantly better initial remission rates have been reported [2, 3]. In this study we have chosen to compare the VCMP combination [17] with standard oral MP treatment, since prospective data concerning survival for VCMP treated patients were not available when this study was launched.

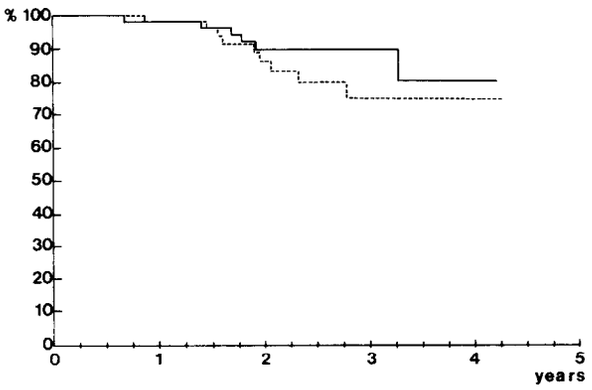

Fig. 4. Survival of patients with primary induction remission. Patients with maintenance (—) versus no maintenance (...) therapy (not significant).

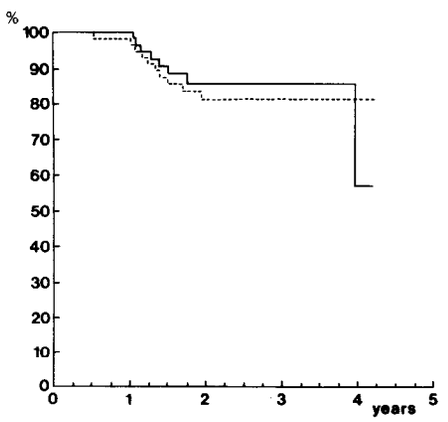

Fig. 5. Probability of acquiring resistance to the first line therapy in maintenance (—) and in no maintenance (...) groups.

In spite of two additional drugs—vincristine and cyclophosphamide—results with VCMP did not differ from MP regarding response rates (Table 2). Similar data have recently been published for a smaller number of patients [25]. Our remission rate after MP treatment corresponded to other MP trials, if the different definitions for response were taken into consideration [3]. The response rates of stage II and stage III patients could not be distinguished from each other, although the latter group showed a more pronounced TCM reduction (Table 3), probably due to their larger compartment of proliferating tumor cells which are usually more sensitive to cytostatic drugs [26].

The tumor cell mass (TCM) calculation method described by Salmon and Wampler [18] appeared to be useful for monitoring in 69% of our patients. In 6% of our patients, contradictory results were obtained using either this TCM calculation or other established criteria for judging treatment results (blood count, performance index, serial X-rays, complications such as hypercalcemia or renal involvement) (Table 4). This divergence may perhaps be explained by a changing subclone composition of the individual tumor resulting in altered rates of monoclonal immunoglobulin synthesis during the course of the disease. We therefore conclude that although the TCM calculation method appears to be well suited for following the majority of patients, other criteria must still be measured prospectively in any multiple myeloma treatment trial, since unexpected developments may not be detected by this method alone, although they may necessitate immediate treatment changes.

Our results with an overall survival probability of 60% 4 years after entering the study compare favorably with earlier trials, surpassing current estimates of average survival by 1 year [3]. Since the participating groups were obliged to enter all newly diagnosed myeloma patients into the study, a selection of patients with a benign disease course can be excluded. In addition, the results obtained with 173 patients collected by five hospitals contributing the majority of patients for the study were evaluated separately; similar results concerning patients' characteristics, remission rate and survival were found in this group. Since the average reduction of TCM after 6 months of treatment amounted to only 66%, an unusual sensitivity to the applied treatment among our patients can also be excluded. The comparatively high survival rate may in part be due to better general patient care, particularly regarding infections and other secondary complications such as thrombocytopenia, hypercalcemic episodes or kidney involvement.

As in other multiple myeloma trials [19], stage II patients on average survived longer than stage III patients (Fig. 1). An unexpected finding was the significantly longer survival of MP treated patients compared to the VCMP group (Fig. 2). The analysis of patients' characteristics in both groups, particularly regarding initial TCM and second line treatment, did not reveal any chance selection in one of the two groups. One hypothetical explanation may be that the VCMP scheme exerted a higher selection pressure for resistant clones; in spite of two additional drugs, and in contrast to other multidrug combinations [3], VCMP did not induce a higher TCM reduction than the MP scheme. Therefore VCMP patients had perhaps less of a chance to respond to salvage treatment using the same or other drug combinations after relapse or progress. No obvious reasons were uncovered for the higher rate of tumor related deaths by renal failure in the VCMP group, a finding of marginal statistical significance which should be carefully followed in future studies with similar drug combinations. On the other hand more MP than VCMP patients died during the induction phase (see Results). If perhaps these patients represent a subgroup with primary resistance to melphalan, they may only have responded to the other drugs contained in the VCMP combination, and might have been selected by individual drug sensitivity testing [27].

After successful remission induction by the six initial treatment cycles, around one third of the initial TCM remained, constituting the pool of cells responsible for later relapse. Even if additional chemotherapy courses might have reduced the TCM further, the problem of consolidation and maintenance therapy would have remained. Based on earlier studies [21, 22], the value of maintenance therapy in multiple myeloma has been questioned, since no obvious survival advantage was observed, and the majority of patients was found to respond again to the primary treatment scheme after relapse. Basically similar results were obtained in our study upon randomization into maintenance and no treatment groups after remission induction. Whereas all patients receiving no further chemotherapy relapsed within three years after commencing treatment, 75% of patients under maintenance therapy were still in remission at this time (Fig. 3). Such pronounced difference has also been reported by Belch *et al.* [21], in contrast to Cohen *et al.* [22] who did not find significant differences in remission duration between MP maintenance and no maintenance treatment, using a different induction therapy (BCNU, cyclophosphamide and prednisone). However, because of the high proportion of secondary responders to the initial treatment scheme after relapse, differences in survival between maintenance and no maintenance groups have not become apparent. In agreement with the other trials we have not noted any difference in developing secondary resistance to the first line therapy between the maintained and the unmaintained treatment groups (Fig. 5). The higher relapse rate in those patients displaying the most pronounced TCM reduction during induction treatment, probably reflects tumors with a comparatively large proportion of actively proliferating cells. For this group of patients, additional methods measuring tumor cell DNA content [28, 29], estimating a tumor cell labelling index [26], or *in vitro* drug testing [27] may constitute important advances towards more effective treatment planning.

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REFERENCES

1. Durie BGM, Salmon SE. The current status and future prospects of treatment for multiple myeloma. *Clin Haematol* 1982, **11**, 181–210.
2. Kyle RA. Treatment of multiple myeloma. A small step forward? *N Engl J Med* 1984, **310**, 1382–1384.
3. Sporn JR, McIntyre OR. Chemotherapy of previously untreated MM patients: analysis of recent treatment results. *Sem Oncol* 1986, **13**, 318–325.
4. McElwain TJ, Powles RL. High-dose intravenous melphalan for plasma-cell leukemia and myeloma. *Lancet* 1983, **II**, 822–824.
5. Alexanian R, Haut A, Khan AU *et al.* Treatment of multiple myeloma. *J Am Med Assoc* 1969, **208**, 1680–1685.
6. Berqsagel DE. Controversies in the treatment of plasma cell myeloma. *Postgrad Med J* 1985, **61**, 109–116.
7. Berqsagel DE, Bailey AJ, Langley GR, MacDonald RN, White DF, Miller AB. The chemotherapy of plasma-cell myeloma and the incidence of a acute leukemia. *N Engl J Med* 1979, **301**, 743–748.
8. Harley JP, Pajak TF, McIntyre OR *et al.* Improved survival of increased risk myeloma patients on combined triple-alkylating agent therapy: a study of the CALGB. *Blood* 1979, **54**, 13–22.
9. Cavagnaro FL, Pavlovsky S, Becherini JO *et al.* Comparison of two combination chemo-

therapy regimens for multiple myeloma: methyl-CCNU, cyclophosphamide and prednisone versus melphalan and prednisone. *Cancer Treat Rep* 1980, **64**, 73–79.
10. Abramson N, Lurie P, Mietlowski WL, Schilling A, Bennet JM, Horton J. Phase III study of intermittent carmutine (BCNU) caclophosphamide and prednisone versus melphalan and prednisone in multiple myelomas. *Cancer Treat Rep* 1982, **66**, 1273–1277.
11. Pavlovksy S, Saslavsky I, Tezanos Pinto M *et al.* A randomized trial of melphalan and prednisone versus melphalan, prednisone, cyclophosphamide, MeCCNU, and vincristine in untreated multiple myeloma. *J Clin Oncol* 1984, **2**, 836–840.
12. Oken MM, Tsiatis A, Abramson N, Glick J. Evaluation of intensive (VBMCP) versus standard (MP) therapy for multiple myeloma. *Proc Am Soc Clin Oncol* 1987, **6**, 203.
13. Salmon SE, Haut A, Bonnet J *et al.* Alternating combination chemotherapy and levamisode improves survival in multiple myeloma: a Southwest Oncology Group study. *J Clin Oncol* 1983, **1**, 453–461.
14. Alexanian R, Dreicer R. Chemotherapy for multiple myeloma. *Cancer* 1984, **53**, 583–588.
15. Case DC, Sonneborn HL, Paul SD *et al.* Combination chemotherapy for multiple myeloma with BCNU, cyclophosphamide, vincristine, melphalan, and prednisone (M-2 protocol). *Oncology* 1985, **42**, 137–145.
16. Cooper MR, McIntyre OR, Propert KJ *et al.* Single sequential, and multiple alkylating agent therapy for multiple myeloma: a CALGB study. *J Clin Oncol* 1986, **4**, 1331–1339.
17. Alexanian R, Salmon SE, Bonnet J, Gehan E, Haut A, Weik J. Combination therapy for multiple myeloma. *Cancer* 1977, **40**, 2765–2771.
18. Salmon SE, Wampler SE. Multiple myeloma: quantitative staging and assessment of response with a programmable pocket calculator. *Blood* 1977, **49**, 379–389.
19. Durie BGM, Salmon SE. A clinical staging system for multiple myeloma. *Cancer* 1975, **36**, 842–852.
20. Alexanian R, Gehan E, Haut A, Saiki J, Weick J. Unmaintained remissions in multiple myeloma. *Blood* 1978, **51**, 1005–1011.
21. Belch A, White D, Bergsagel D, Wilson K, Shelley W. The role of maintenance chemotherapy for multiple myeloma. *Proc Am Soc Clin Oncol* 1984, **3**, 268.
22. Cohen HJ, Bartolucci AA, Forman WB, Silberman HR. Consolidation and maintenance therapy in multiple myeloma. *J Clin Oncol* 1986, **4**, 888–899.
23. Peest D, Schmoll HJ, Schedel I *et al.* Current results of a multicenter trial in multiple myeloma. *Oncology* 1986, **9**, 168–169.
24. Peest D, Schmoll HJ, Schedel I, Glück S, Schumacher K, Deicher H. VBAMDex chemotherapy in advanced multiple myeloma. *Eur J Haematol* 1988, in press.
25. Tribalto M, Amadori S, Cantonetti M *et al.* Treatment of multiple myeloma: a randomized study of three different regimens. *Leukemia Res* 1985, **9**, 1043–1049.
26. Drevinko B, Alexanian R, Boyer H, Barlogie B, Rubinow SI. The growth fraction of human myeloma cells. *Blood* 1981, **57**, 333–338.
27. Peest D, Bartels B, Dallmann I, Schedel I, Deicher H. Cytostatic drug sensitivity test for human multiple myeloma, measuring monoclonal immunoglobulin produced by bone marrow cells *in vitro*. *Cancer Chemother Pharmacol* 1986, **17**, 69–74.
28. Barlogie B, Alexanian R, Dixon D, Smith L, Smallwood L, Delasalle K. Prognostic implications of tumor cell DNA and RNA content in multiple myeloma. *Blood* 1985, **66**, 338–341.
29. Hein R, Schedel I, Schmiedel D *et al.* Aneuploid cells in human myeloma—immunological characterization and clinical implications. *Immunobiology* 1985, **170**, 28.