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Melphalan-prednisone versus alternating combination VAD/MP or VND/MP as primary therapy for multiple myeloma: final analysis of a randomized clinical study

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Background and Objectives. In the absence of a cure for multiple myeloma (MM) with standard-dose therapy, any strategy that can be expected to increase tumor reduction and to extend survival duration is likely to be of clinical relevance. The primary end-point of the present study was to investigate whether the alternating combination of vincristine-doxorubicin-dexamethasone (VAD) and melphalan-prednisone (MP) or vincristine-mitoxantrone-dexamethasone (VND) and MP could improve the clinical outcome of MM patients thus treated in comparison with those receiving MP alone.

Design and Methods. Between November 1990 and April 1994, 527 previously untreated, stage I-III, MM patients from 29 Italian institutions were randomized to receive one of three remission induction chemotherapy regimens consisting of 8-monthly courses of either MP alone or alternating VAD/MP or VND/MP.

Results. On an intent-to-treat basis, the objective response rates were 53% with MP (objective + minor: 67%), 47% with VAD/MP (objective + minor: 61%) and 49% with VND/MP (objective + minor: 61%). Median survival duration was 36.5 months with MP, 29 months with VAD/MP and 32.5 months with VND/MP. The difference among these groups was not statistically significant, even after stratifying patients into high-risk and low-risk subgroups, as assessed by a multifactor proportional hazard analysis. In both younger and elderly patients, severe granulocytopenia and related infections were significantly more frequent with VND/MP compared to the remaining arms of treatment ($p < 0.001$ and $p = 0.009$, respectively). Similarly, the frequency of WHO grade III-IV cardiovascular events was significantly higher for patients receiving anthracycline-containing regimens (VND/MP and VAD/MP) than for those treated with MP alone ($p = 0.04$).

Interpretation and Conclusions. Alternating VAD/MP and VND/MP failed to improve the clinical outcome for MM patients, at the cost of increased toxicity and morbidity. Resistance to standard-dose chemotherapy remains a significant obstacle to the treatment of MM.

Key words: multiple myeloma, standard-dose primary chemotherapy, melphalan-prednisone, VAD, randomized study.

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Progress toward improving the prognosis of multiple myeloma (MM) with standard-dose therapy has been modest since the early 1960s. Intermittent melphalan-prednisone (MP) is still considered at many centers the treatment of choice for patients not eligible for high-dose therapy. It produces a response rate of approximately 50-55% and a median survival averaging 3 years.[1] Extensive clinical trials exploring the use of multiple cytotoxic drugs administered at doses inducing only mild myelosuppression have failed to improve clinical outcome consistently.[1,2] As a result, stringently defined complete remission (CR) rates have not exceeded 5% and cure still remains an elusive goal in MM. More recently, several advances in the conventional management of the disease have been reported, including the efficacy of high-dose glucocorticoids administered alone or combined with continuously infused vincristine and doxorubicin (VAD) for patients in whom prior alkylating agent chemotherapy has failed.[3-6] Favorable results initially obtained with VAD in melphalan-refractory MM provided the incentive for subsequent clinical trials using this regimen in previously untreated patients.[6-9] More rapid cytoreduction with VAD in comparison with MP was generally observed, reflecting the different activity of these treatments against more or less mature myeloma cell subpopulations, respectively.[8] How-

ever, shortcomings of VAD, particularly the occurrence of serious infections[6-9] and cardiovascular complications,[5] were reported in most studies and led to phase I-II clinical trials aimed at exploring the efficacy of VAD-hybrids.[10,11]

In the absence of a cure for MM with standard-dose therapy, any strategy that can be expected to increase tumor reduction and to extend survival duration is likely to be of clinical relevance. In the search of more effective treatments for remission induction, in 1990 we designed the randomized clinical trial *Bologna 90* which was based on an alternating sequence of VAD and MP or VND (a VAD-hybrid modified by substituting doxorubicin with mitoxantrone) and MP. The primary end-point of this study was to assess whether the alternating combinations VAD/MP and VND/MP could improve the clinical outcome in comparison with MP alone. As a secondary end-point the toxicity profile of the novel VND/MP regimen was investigated.

Design and Methods

Selection and accrual of patients

Between November 1990 and April 1994 a total of 542 patients with previously untreated MM from 29 Italian institutions were registered in the *Bologna 90* clinical trial. The diagnosis of MM was established according to the criteria of the *Chronic-Leukemia Myeloma Task Force*.[12] Patients were eligible for randomization if they had symptomatic MM and measurable M-protein in the serum and/or urine. Reasons for exclusion included age > 80 years, severe heart disease, hepatic dysfunction or prior history of another neoplasm. Patients with smoldering myeloma, localized plasmacytoma or plasma cell leukemia were also excluded. Treatment assignments were stratified for clinical stage. Patients were randomly assigned to treatment in blocks of six by a computer-generated series of random numbers. All patients gave verbal or written consent before being entered into the study.

Study design

For remission induction treatment, patients were randomized to receive one of three regimens consisting of either MP alone (arm A) or VAD alternating with MP (arm B) or VND alternating with MP (arm C). Randomization to the three arms of the study was 1:1:1. Patients were planned to receive 8-monthly courses of chemotherapy; in arms B and C the first course of treatment consisted of VAD and VND, respectively. Melphalan and prednisone were administered at the doses of 10 mg/m^2 orally and 80 mg/m^2 i.m, respectively, on days 1 to 4. The VAD regimen included vincristine and doxorubicin, both administered by continuous i.v. infusion at the doses of 0.4 mg/d and 9 mg/m^2/d, respectively, on days 1 to 4, and an added 4-day pulse of dexamethasone at the dose of 40 mg/d. The VND regimen was identical to VAD except for the substitution of doxorubicin with mitoxantrone (Novantrone, Lederle) which was administered by continuous i.v. infusion at the dose of 3 mg/m^2/d, on days 1 to 4. Full drug doses were administered if granulocytes > 2×10^9/L and platelets > 100×10^9/L. A graded dose reduction scheme was used for lower granulocyte and/or platelet counts according to the National Cancer Institute's proposed guidelines for anticancer drugs. Oral ciprofloxacin was administered as antimicrobial prophylaxis. Treatment cycles were repeated every 28 days if blood counts permitted; when required for hematologic recovery, the interval between chemotherapy courses was increased, usually to 35-42 days and occasionally longer. Patients who completed the induction chemotherapy phase of the study and achieved an objective response (see response criteria section) received recombinant interferon (IFN) α-2b (Intron A, Schering-Plough, Italy) at the dose of 3 MU, subcutaneously, three times weekly, until evidence of progression.

Sample size estimation

The primary objective of the *Bologna 90* clinical trial was to compare standard MP with the alternating combinations VAD/MP and VND/MP with respect to the probability of response. A 15% difference in the response rate (55% in the control group vs 70% in the alternating combination regimens) was considered of clinical interest. Assuming a significance level $\alpha = 0.05$ and a power = 0.90, the estimated sample size necessary to demonstrate such a difference was in the order of 520 patients.

Follow-up evaluations

All patients were regularly seen at intervals of 28 days for clinical and laboratory evaluation. Routine laboratory tests included complete blood cell counts, protein electrophoresis of serum and/or 24-hour urine collection and blood tests of hepatic and renal function. The degree of myelosuppression induced by conventional chemotherapy was checked by measuring granulocyte and platelet counts at day +14 after the start of each course of chemotherapy. Complete restaging, including blood counts, chemistries, serum and urine immunoglob-

ulin levels, repeat bone marrow aspirate and skeletal X-ray survey, was performed at the end of induction chemotherapy and results were reported to the co-ordinating center.

Hematologic and non-hematologic toxicity was carefully registered after each treatment cycle according to WHO criteria.[13]

Response criteria

Response was evaluated according to the criteria of the *Chronic-Leukemia Myeloma Task Force*[12] and was based on M-protein decrease at the end of induction chemotherapy as compared with pretreatment values. For those patients who did not complete the induction chemotherapy phase of the study, response was graded on the basis of the best reduction in M-protein concentration achieved on at least two successive determinations at 4-week interval. Patients who did not have sufficient follow-up information to permit assessment of their response were considered to be non-responders. An objective response was defined by a decrease in serum or urinary M-protein concentration of at least 50% or 75%, respectively, without other evidence of progression. Patients who achieved only a 25% to 50% decrease in serum M-protein level or at least 50% reduction in 24-hour excretion of urinary light chains were considered as having a minor response. Criteria for stable disease, or no change, included less than 25% decrease in serum M protein level or less than 50% reduction in Bence Jones proteinuria. A plateau phase was considered to be present if three consecutive measurements of M-protein concentration performed at intervals of at least every 4 weeks varied by less than 15%. Progression was defined as a confirmed increase in M-protein concentration of more than 25% above pretreatment values (for patients registered in the induction chemotherapy phase of the study) or above the nadir values (for patients registered in the postinduction chemotherapy phase of the study) and/or an increase in size or number of lytic bone lesions either during or after completion of induction chemotherapy.

Dose intensity

The relative dose intensity for melphalan, prednisone, doxorubicin and mitoxantrone was calculated for each patient by dividing the cumulative dose intensity actually received over the period of treatment by the cumulative dose intensity that had been planned over the same period according to the study protocol. Average relative dose intensity was calculated by methods previously described.[14]

Statistical methods

The present report is based on follow-up data as of October 2001. At this time, the median follow-up from the start of remission induction chemotherapy was 31.5 months for all patients and 48 months for living patients. Comparisons between treatment arms at randomization were made using the Wilcoxon rank-sum test for continuous parameters and the χ^2 test for dichotomous parameters. The χ^2 test was used to assess the statistical significance of the response rate to remission induction treatment. Survival was calculated from the date of randomization into the remission induction chemotherapy phase of the study to the date of last follow-up or death. Patients with relapsed/progressive MM who received salvage autologous transplantation were censored at the time of transplant. The duration of response for patients achieving an objective response was determined from the date of registration onto IFN maintenance until the time of progression. Curves for overall survival were plotted according to the method of Kaplan and Meier[15] and were compared by the log-rank test.[16] To overcome the bias introduced by the *guarantee time* of responders (e.g. the time required to detect the response), the influence of response to induction chemotherapy on the survival duration was assessed by the Mantel and Byar method.[17] Prognostic factors for overall survival were determined by logistic regression analysis or the Cox proportional hazards model.[18] The following variables, which were available for more than 80% of patients, were included in the model: age, sex, performance status, hemoglobin, platelets, albumin, creatinine, bone marrow plasma cell infiltration, Durie & Salmon clinical stage, β2-microglobulin (β2-M), arm of treatment, average relative dose intensity and response to remission induction treatment. This last variable was incorporated into the Cox model as a time-dependent covariate. A two-tailed *p* value (< 0.05) was considered statistically significant.

Results

Patients' characteristics

A total of 543 patients were registered for the trial; of these, 16 either lacked eligibility criteria or had inadequate baseline information and were not randomized to the three treatment arms. Of the 527 eligible patients, 179 were randomly assigned to arm A (MP), 174 to arm B (alternating VAD/MP) and 174 to arm C (alternating VND/MP). Clinical and laboratory characteristics of the patients at the time of registration into the study are shown

in Table 1. No statistically significant difference among the three treatment groups was observed with respect to the most relevant variables presumed to have prognostic significance.

Response to remission induction treatment

All patients who were randomly assigned to receive one of the three treatments of the study were evaluated for response according to the principle of intention-to-treat. Overall, the probability of attaining an objective response (objective + minor) was 53% (67%) with MP, 47% (61%) with alternating VAD/MP and 49% (61%) with alternating VND/MP (Table 2). The difference between the three groups did not reach statistical significance. The median time from randomization to objective response was 104 days for arm A (MP), 111 days for arm B (VAD/MP) and 109 days for arm C (VND/MP).

The median relative dose intensity for melphalan was 0.75 in arm A, 0.76 in arm B and 0.73 in arm C. The median relative dose intensity for prednisone was 0.75 in arm A, 0.76 in arm B and 0.71 in arm C. The median relative dose intensity for doxorubicin and mitoxantrone was 0.86 each. The proportion of patients having an average relative dose intensity ≥ 0.80 was 64% in arm A, 71% in arm B and 64% in arm C.

Survival

At the time of the present analysis, the number of patients who had died was 144 (80%) in the MP group, 148 (85%) in the VAD/MP group and 137 (79%) among those treated with VND/MP. Figure 1 shows the probability of survival for patients assigned to receive the three treatments of the study. The median survival duration was 36.5 months for patients on MP, 29 months for patients on VAD/MP and 32.5 months for patients on VND/MP. The difference was not statistically significant for the three-group comparison, nor for the arm A (MP) versus arm B (VAD/MP) comparison and for the arm A versus arm C (VND/MP) comparison. Closer examination of the curves revealed that the proportion of patients who died from any cause during the first 3 months from registration into the study was 3.4% in arm A, 6.9% in arm B and 8.6% in arm C ($p = 0.04$ for arm C versus arm A+B comparison). When the analysis of early deaths was limited to patients aged ≥ 60 years, the corresponding figures for the three treatment groups were 7.4%, 7.9% and 9.9%, respectively.

Results of analyses of risk factors for overall survival are summarized in Table 3. To discern the independent contribution to clinical outcome of variables found to be relevant in univariate analysis, a multivariate regression analysis was performed. The following factors were found to be independently associated with extended survival: response (objective + minor) to remission induction treatment ($p < 0.001$), β2-M ≤ 4 mg/L ($p < 0.001$), platelet count >150×10⁹/L ($p < 0.001$), performance status grade 0-2 ($p < 0.001$), average relative dose intensity ≥ 0.80 ($p = 0.0004$), bone marrow plasma cell infiltration ≤ 60% ($p = 0.0007$), female sex ($p = 0.001$), age ≤ 60 years ($p = 0.002$), and Durie & Salmon stages I and II ($p = 0.01$).

Table 1. Patients' characteristics at time of randomization to receive the three treatments of the study.

Characteristics	*% of patients* *MP (n=179)*	*VAD/MP (n=174)*	*VND/MP (n=174)*
Sex (male/female)	50/50	51/49	57/43
Age ≤ 60/> 60 years	41/59	40/60	44/56
PS grade 0-2/3-4	68/32	63/37	65/35
M component			
IgG	65	54	56
IgA	24	28	26
BJ	10	15	16
Other	1	3	2
Stage I/II/III	15/22/63	14/18/68	12/20/68
β2-M ≤4/> 4 mg/L	56/44	52/48	50/50
Albumin > 3/≤ 3 g/dL	82/18	84/16	89/11
CRP ≤ 6/> 6 mg/L	51/49	59/41	57/43
Hb > 10.5/≤ 10.5 g/dL	49/51	53/47	51/49
PLTs > 150/≤ 150×10⁹/L	85/15	76/24	79/21
Bone marrow PC ≤ 60/> 60%	53/47	55/45	56/44

Abbreviations: PS, performance status; β2-M, β2-microglobulin; CRP, C-reactive protein; Hb, hemoglobin; PLTs, platelets; PC, plasma cells.

Table 2. Response to the three treatments of the study.

	N° of patients (%) *MP (n=179)*	*VAD/MP (n=174)*	*VND/MP (n=174)*
Objective response	95 (53)	82 (47)	86 (49)
Minor response	25 (14)	24 (14)	21 (12)
No change	28 (16)	38 (22)	34 (20)
Progression	31 (17)	30 (17)	33 (19)

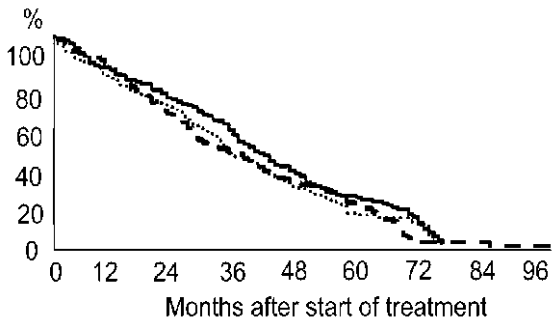

Figure 1. Probability of survival for patients randomized to receive MP (—)or VAD / MP (- - -)or VND / MP (– – –) (*p*, not significant).

Since the survival curves of patients attaining objective response or minor response were almost superimposable, both these groups were pooled together (responders) and analyzed in comparison with patients who either had no change or who progressed (non-responders). A significant advantage in favor of the responder group was observed using both the standard survival analysis ($p < 0.001$) and the Mantel and Byar test ($p < 0.001$). Of note, survival duration of patients who entered a plateau phase was significantly shorter than that of patients who responded to treatment ($p = 0.009$) or who progressed ($p = 0.007$).

Toxicity and adverse events

The major toxicity was hematologic, particularly granulocytopenia. Absolute granulocyte counts ≤ 1×10^9/L were recorded in 39% of cycles in arm C as opposed to in 18% of cycles in arm B and 15% of cycles in arm A (Table 4). Comparisons between the three treatment arms were statistically significant in the entire series of patients ($p < 0.001$), as well as in younger (≤ 60 years) and elderly patients ($p < 0.001$ in both groups). In arms B and C moderate to severe granulocytopenia (< 1×10^9/L) was recorded more frequently in association with anthracycline-containing regimens than with MP (arm B: $p = 0.001$; arm C: $p < 0.001$). As a result of the more frequent and severe granulocytopenia associated with VND, the proportion of patients who suffered from infections was significantly higher in arm C (VND/MP) than in arms B and A (23% vs. 14% vs. 10%, respectively; $p = 0.009$). However, no statistically significant difference was observed between the number of deaths due to infection in the three treatment groups.

Table 3. Analysis of risk factors on overall survival.

Variable	Univariate analysis χ^2	Univariate analysis p value	Multivariate analysis χ^2	Multivariate analysis p value	Regr. coeff.
Response (objective + minor) vs no response	73.30	<0.001	86.49	<0.001	-1.0045
β2-M ≤ 4 vs > 4 mg/L	54.39	<0.001	75.38	<0.001	0.7342
PLTs ≤ 150 vs > 150×10^9/L	27.54	<0.001	26.21	<0.001	-0.6674
Performance status grade 0-2 vs 3-4	33.41	<0.001	26.52	<0.001	0.4868
Av Rel DI ≤ 0.80 vs > 0.80	28.47	<0.001	12.39	0.0004	-0.5671
Bone marrow PC ≤ 60 vs > 60%	17.46	0.0003	11.28	0.0007	0.4309
Sex F vs M	12.78	0.0003	9.79	0.001	-0.4688
Age ≤ 60 vs > 60 years	4.71	0.029	9.06	0.002	0.3906
Stage I-II vs III	25.20	<0.001	5.85	0.01	0.3802

Regr Coeff, regression coefficient; β2-M, β2 microglobulin; PLTs, platelets; Av Rel DI, average relative dose intensity; PC, plasma cells.

Table 4. WHO grade III-IV granulocytopenia.

	N° cycles with toxicity (%) / N° evaluable cycles			
	Arm A (MP)	Arm B (VAD/MP)	Arm C (VND/MP)	p value
Cycles 1 to 8	165/1121 (15%)	189/1070 (18%)	364/941 (39%)	<0.001
Cycles 1, 3, 5, 7*	87/578 (15%)	116/542 (21%)	314/473 (66%)	<0.001
Cycles 2, 4, 6, 8°	78/543 (14%)	73/528 (14%)	50/468 (11%)	0.1
Age ≤ 60 yrs	82/647 (13%)	89/623 (14%)	225/578 (39%)	<0.001
Age > 60 yrs	83/474 (17%)	100/447 (22%)	139/363 (38%)	<0.001

**MP, in Arm A; VAD, in Arm B; VND, in Arm C; °MP in Arms A, B and C.*

The major non-hematologic toxicity was cardiac. Two patients enrolled in arm A (MP) suffered from WHO grade III-IV cardiac toxicity in comparison with 15 patients receiving VAD/MP (n=6) or VND/MP (n=9) ($p = 0.04$). Of these 15 patients, 5 were aged < 65 years and 10 were older ($p = 0.04$). Cardiovascular events included congestive heart failure (14 patients), unstable angina (2 patients) and myocardial infarction (1 patient).

IFN maintenance and salvage treatment

Two hundred and nineteen patients who completed the remission induction chemotherapy phase of the study and fulfilled the criteria for objective response received IFN maintenance therapy. The majority of them (62%) were able to receive 100% of the planned dose consisting of 3 MU three times weekly. A reduction of 25% to 50% of the scheduled dose was required in 38% of the patients. Thirty-seven patients (17.5%) discontinued IFN treatment, mainly due to poor tolerance or

toxicity. At the time of the present analysis, there had been 156 (71%) deaths and 190 (87%) relapses; the median duration of remission from the start of IFN maintenance was 9.0 months. Salvage standard-dose therapy for patients relapsing on IFN generally included intermediate-dose cyclophosphamide plus steroids; no difference was observed in the rate of response to cyclophosphamide and the duration of survival calculated from the start of salvage therapy between the three treatment groups. After the superiority of autologous stem cell transplantation over standard-dose therapy had been clearly demonstrated,[19] younger patients (≤ 65 years) with progressive disease were offered salvage autotransplantation, provided an adequate number of peripheral blood stem cells (PBSC) was collected following priming therapy with high-dose cyclophosphamide (7 g/m^2) and granulocyte colony-stimulating factor (G-CSF). PBSC collections and autotransplant outcomes were similar in arms A, B and C of the study.

Discussion

The present clinical trial was designed in 1990 in an attempt to maximize the potential benefits of the two most popular remission induction regimens in use for the treatment of MM, namely MP and VAD. For this purpose a sequence of alternating courses of VAD or its hybrid VND and MP was administered to a large cohort of patients with newly diagnosed disease. The rationale for this treatment strategy adhered to the principles emphasized by Goldie and Coldman[20] and rested on the hypothesis that different myeloma cell subpopulations may be targeted by MP and VAD. In particular, MP may be more active against less differentiated myeloma precursor cells, whereas VAD may affect primarily mature plasma cells. Based on this assumption, we hoped that the alternating combination of VAD/MP or VND/ MP could improve on the results obtained with each of these regimens alone by providing differential tumor cell killing. Moreover, we reasoned that early exposure to active, non-cross-resistant treatments might prevent evolution of resistant clones.[21]

Data from the final analysis of the *Bologna 90* clinical trial show that this was not the case since we were unable to demonstrate any gain in either the response rate or survival duration with alternating drug combinations in comparison with MP. Moreover, combined chemotherapies were associated with increased hematologic and non-hematologic toxicity.

The lack of any benefit from VAD/MP and VND/MP was disappointing, particularly since VAD was previously shown to produce the highest rate of response for patients in whom MP had failed.[4,5] Several hypotheses can be raised to explain these negative results. First, we omitted the second and third dexamethasone pulses (i. e. on days 9-12 and 17-20) in each VAD and VND cycle in an attempt to reduce the frequency of serious infections reported in earlier clinical studies.[4,8] It is generally believed that the activity of VAD is primarily attributable to high-dose dexamethasone.[22] In accordance with the importance of intensive glucocorticoid administration, a recent randomized SWOG study demonstrated a significant gain from chemotherapy regimens including higher dose-intensity glucocorticoids.[23] In our trial, dexamethasone dose-intensity was lower than that reported in previous studies with VAD[7-9] or its hybrids,[11] a finding that may have adversely affected the therapeutic results. Second, in comparison with MP, alternating combinations, particularly VND/MP, resulted in increased morbidity and early mortality that could have ultimately influenced the clinical outcome.

Results of the present analysis were consistent with those of a similar study performed in stage III MM[24] and with data of recently published trials aimed at comparing MP versus combined chemotherapy.[2,25] A meta-analysis of most of these trials failed to disclose any advantage on 2-year survival rate from combined chemotherapy.[1] However, in that study there was an implication that MP was superior to combined chemotherapy for patients with intrinsically good prognosis and inferior for patients with poor prognosis. To explore this possibility, we compared the three treatment arms of the study by stratifying patients into low- and high-risk subgroups, as assessed by a multivariate regression analysis. Again, we were unable to demonstrate that, for any prognostic parameter, there was a group of patients who did better, or worse, when allocated to a particular type of chemotherapy. More specifically, there was no evidence that high-risk patients benefitted more from combined chemotherapy, in accordance with the results of an overview of more than 6,000 patients recently reported by the Myeloma Trialist's Collaborative Group.[2]

In the present study stratification of patients into low- and high-risk subgroups was based on the results of a multivariate analysis indicating that β2-M, performance status, bone marrow plasma cell infiltration, sex, age and clinical stage were independently associated with overall survival. In

addition, we provided a demonstration of the predictive power of platelet count, a finding previously recognized by our group[26] and subsequently confirmed by others.[27,28] Also a higher received average relative dose intensity was a favorable variable for prolonged survival. Of note, when response to therapy was included into the Cox model as a time-dependent covariate, along with additional presenting clinical and laboratory parameters, it emerged as a dominant favorable variable. Although the relationship between response to treatment and prognosis has been a central feature of MM literature since the early 1970s,[29] several authors have recently questioned whether changes in serum and/or urinary M protein level reliably predict survival of MM patients.[30-31] Moreover, the appropriateness of usual statistical methods for analyzing the impact of treatment response on survival duration has also been questioned.[30] The present analysis showed that survival curves of patients attaining either objective response or minor response merely overlapped and differed significantly from the survival curve of patients who were categorized as non-responders. Within this latter group, patients with no change in their M protein level (i. e. in the plateau phase) had a significantly poorer prognosis than responders. The relationship between tumor response and survival duration was further demonstrated using the Mantel & Byar test which eliminates the bias in favor of responders represented by the *guarantee time*.[17]

In previous studies, treatment of MM patients with VAD was reported to be associated with considerable morbidity, particularly infective[4,6,8,9,32] and cardiovascular.[5,32] As a result of these complications, we investigated a VAD-hybrid regimen by substituting doxorubicin with mitoxantrone (VND). The rationale for this treatment strategy relied upon showing that bolus mitoxantrone was active for the treatment of refractory MM[10] and had lower cardiotoxicity than doxorubicin.[33] In order to have careful comparisons of the activity and toxicity of VND with those observed among patients receiving continuously infused VAD, we administered mitoxantrone by continuous infusion. VND cycles were alternated with MP and the results of this novel remission induction regimen (VND/MP) were compared with those of alternating VAD/MP and MP alone. Myelosuppression, particularly granulocytopenia, was the major toxicity associated with VND. Consequently, increased infective morbidity was more commonly observed in patients randomized to arm C of the study than in those randomized to the other treatment arms. Granulocytopenia, albeit severe, was transient and no reduction in the received average relative dose intensity was observed with VND/MP. Increased myelosuppression induced by VND was not unexpected since the dose of mitoxantrone was higher than would be defined equipotent to doxorubicin in VAD. Consistently with our findings, in a recently reported study on mitoxantrone administered as bolus injection together with vincristine and prednisone, grade III-IV hematologic toxicity was recorded in up to 80% of patients, of whom 15% suffered from one or more episodes of grade III cardiotoxicity.[10] Cardiovascular morbidity was also a major concern with alternating VAD/MP and VND/MP and was not lowered with VND in comparison with VAD. As far as this last issue is concerned, it should be emphasized that several factors other than anthracycline-related cardiotoxicity could contribute to cardiovascular morbidity, including the concomitant administration of high-dose glucocorticoids[5] and/or the simultaneous occurrence of infective complications.[10]

In conclusion, the results of the *Bologna 90* clinical trial did not show any advantage in either response rate or survival duration from alternating administrations of continuously infused anthracycline-containing regimens and MP over MP alone as remission induction chemotherapy for newly diagnosed MM. Moreover, combined chemotherapy may have been harmful by producing increased toxicity and related morbidity. Resistance to standard-dose chemotherapy continues to be a major obstacle to improving the prognosis of MM patients. Newer drugs targeting both the tumor cells (e.g. their growth and apoptosis) and the bone marrow microenvironment[34,35] are currently under investigation in phase II-III clinical trials and hold promise to circumvent, at least in part, chemoresistance. These drugs, both alone and in combination with cytotoxic agents, represent promising paradigms in the management of MM in the near future.

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MC and ST designed the study, interpreted the results and drafted the article. MB, SR, AG, EZ and CC collected and analyzed data. MF and PT analyzed data and reviewed the article. MB and ST gave the final approval of the version to be published.

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Appendix

List of additional authors who participated in the study

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PEER REVIEW OUTCOMES

Manuscript processing

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What is already known on this topic

Several combinations of chemotherapeutic agents have been used for multiple myeloma.

What this study adds

The combination of chemotherapeutic agents used here (alternating VND/MP and VAD/MP) failed to improve the clinical outcome of MM patients.

Potential implications for clinical practice

MP continues being the gold standard for patients who are not candidates to stem cell transplantation.

Jesus San Miguel, Associate Editor