Prednisone Pulse Therapy for Refractory Myeloma

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The utility of vindesine and a frequent prednisone schedule was evaluated in 70 patients with refractory myeloma. No patient responded to vindesine alone, but about one-fourth achieved significant tumor reductions from intermittent high-dose prednisone, either alone or in combination with vindesine. Forty-seven percent responded when prednisone pulses were combined with vincristine and doxorubicin, providing the best results yet achieved in our patients with refractory myeloma. In responding patients, remissions were of excellent quality and survival was prolonged significantly. These results supported the utility of a more frequent corticosteroid schedule with increased doxorubicin dose in patients with advanced and resistant multiple myeloma.

VERY FEW TREATMENT programs have shown any benefit in patients with multiple myeloma resistant to intermittent melphalan-prednisone or similar drug combinations. Doxorubicin and nitrosourea combinations, cyclophosphamide, hexamethylmelamine, and human leukocyte interferon have benefitted small percentages of patients.[1-7] Recently, Houwen et al. reported responses in 6 of 11 patients with refractory myeloma who had received weekly courses of vindesine-prednisone,[8] alhough in a larger series, only 25% responded.[9] Our report describes further evaluations of vindesine-prednisone in patients with multiple myeloma and indicates that the remissions result primarily from the frequent prednisone courses. With a regimen that combined vincristine, doxorubicin, and frequent prednisone, about one-half of myeloma patients with advanced refractory disease achieved tumor reductions of at least 50%. This result was superior to any previously achieved in our patients with resistant myeloma.

MATERIALS AND METHODS

Between August 1980 and October 1982, 70 patients with multiple myeloma and unequivocal resistance to melphalan-prednisone combinations were treated and completed 73 trials of vindesine alone, vindesine with prednisone, prednisone alone, or a combination of vincristine-prednisone-doxorubicin. Table 1 summarizes the clinical features of these patients with advanced and refractory disease, all of whom had received various intermittent combination therapies until 4 wk prior to these trials. Patients with nonsecretory myeloma were ineligible because there was no myeloma protein marker from which to evaluate response. Previously unresponsive patients with a low and stable tumor mass were ineligible because they were asymptomatic and had a good prognosis. At the time of treatment, 3% of patients were hypercalcemic (>11.5 mg/dl) and 5% were azotemic (creatinine >2.0 mg/dl). The median duration of prior chemotherapy was 16 mo for unresponsive patients and 46 mo for those relapsing from prior remissions.

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Submitted October 25, 1982; accepted March 28, 1983.

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0006-4971/83/6203-0008$01.00/0

There were four phases to the study. Initially, 11 consecutive patients were treated with vindesine alone; then 16 consecutive patients received vindesine-prednisone; then 16 consecutive patients were treated with prednisone pulses alone; and finally, 30 consecutive patients received a vincristine-doxorubicin-prednisone program. (Three patients treated with vindesine alone were also registered on one later trial that included prednisone.) All trials included serial measurements of blood counts, multichemical scan and electrophoretic data, and calculations of tumor mass change and survival from the start of treatment. "Response" was defined by a 75% reduction, and "improvement" by a 50%–74% reduction of tumor mass and disappearance of Bence Jones protein excretion.[10] Changes in tumor mass were calculated from changes in myeloma protein production; this assessment considered the serum myeloma protein concentration, the changing IgG catabolic rate with falling level, the estimated plasma volume, and the background of normal gamma globulin. Nine of the 70 patients died during the first 2 mo of treatment and were considered unresponsive. Patients responding to vindesine-prednisone or prednisone alone were maintained on monthly courses of intermittent melphalan (7 mg/sq m/day for 4 days) and prednisone (60 mg/sq m/day for 4 days); patients responding to vincristine-doxorubicin-prednisone were maintained on monthly courses of vincristine-cyclophosphamide-doxorubicin-prednisone with a lower doxorubicin dose and prednisone given in a standard 4-day schedule.[10] Survival curves were calculated by life table analysis.

RESULTS

Vindesine Alone

Eleven patients received 3 intravenous injections of vindesine alone (1.8 mg/sq m at 8-day intervals). After a 3-wk rest, a second and then a third series of injections were given with 25% dose increments, depending on the degree of neurotoxicity and/or granulocytopenia. All patients experienced moderate degrees of either granulocytopenia (<1,500 cu mm) or peripheral neuropathy which were reversible. Of the 11 treated patients, 6 had been unresponsive and 5 relapsing to prior chemotherapy, which had included vincristine in all patients. As indicated in Table 2, none showed a 50% reduction in myeloma protein level.

Vindesine Plus Prednisone

As the negative results from vindesine alone became apparent, 16 additional patients received a treatment program virtually identical to that found useful by Houwen et al.[8] This consisted of, in addition to vindesine, prednisone, 60 mg/sq m/day for 5 days, repeated

Table 1. Pretreatment Features of Patients

No. patients	70
Males (%)	40
Age (median)	59
Laboratory data	
% Hemoglobin <9 g/dl	33
% Serum peak >5 g/dl	22
Myeloma proteins	
IgG	62
IgA	27
Only Bence Jones protein	11
Median survival (mo)	11
Tumor mass	
% High	43
% Intermediate	43
% Low	14*

*All were treated during early relapse with a subsequent median survival of 12 mo.

for 3 pulses at 8-day intervals, again with a 3-wk interval between cycles. Three previously unresponsive patients achieved a 75% or greater reduction of myeloma protein, and one patient "improved," resulting in a 25% response rate (Table 2). Figure 1 demonstrates the marked tumor reductions in three patients. (Three patients unresponsive to vindesine alone were registered on later trials with prednisone: one responded to vindesine-prednisone, one responded to prednisone alone, and one was unresponsive to vincristine-doxorubicin-prednisone. No other patients were included in multiple trials.)

Prednisone Alone

As partial remissions were confirmed from the vindesine-prednisone combination, 16 additional patients were treated with 5-day prednisone pulses alone in the same intermittent dose regimen (60 mg/sq m/day) and 3-wk interval between cycles, as described previously. Of the 16 treated patients, 3 responded with

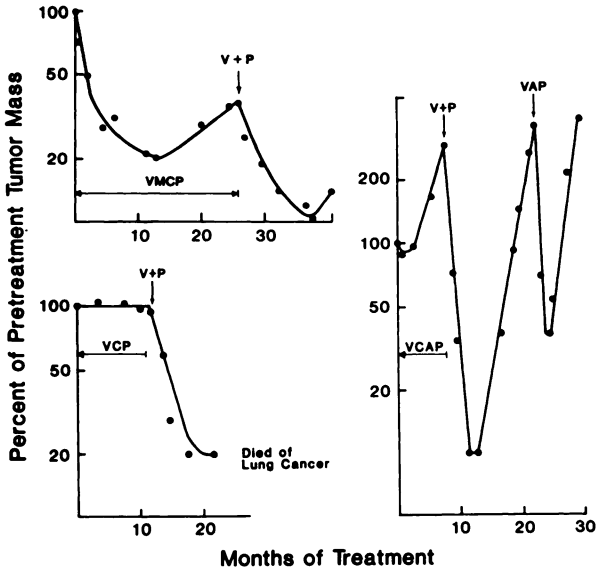

Fig. 1. Changes in myeloma tumor mass from chemotherapy. Each panel shows tumor response from weekly vindesine-prednisone (V + P) in patients resistant to monthly courses of vincristine-alkylating agent-prednisone chemotherapy. V, vincristine; M, melphalan; C, cytoxan; P, prednisone; A, doxorubicin. Data in the upper left panel were from one relapsing patient and that on the lower left and right panels from nonresponders with progressive disease. One of the latter died in remission of bronchogenic cancer, while the other responded again to the later addition of doxorubicin.

75% tumor mass reductions and 2 patients "improved," resulting in a 31% response rate (Table 2). These patients included four patients unresponsive and one relapsing to prior chemotherapy (Fig. 2). One patient who had failed on vindesine alone, and who had then developed severe panyctopenia from marked bone marrow plasmacytosis, responded to prednisone pulses alone. Of the 9 patients responsive to pulse prednisone (with or without vindesine), all had been resistant to prior alkylating agents and 5 had been resistant to

Table 2. Vindesine and/or Prednisone Pulse Therapy for Refractory Myeloma*

	Previously Unresponsive	Previously Relapsing	Tumor Mass Reduction >75%	Tumor Mass Reduction >50%
Vindesine				
1.8 mg/sq m/every 8 days × 3 injections repeated after 3 wk rest	0/6	0/5	0/11	0/11
Vindesine-prednisone				
Vindesine as above; prednisone 60 mg/sq m/day × 5 days, every 8 days × 3 pulses, and repeated after 3 wk rest	3/11	0/5	3/16	4/16 (25%)
Prednisone alone				
60 mg/sq m/day × 5 days, every 8 days × 3 pulses, and repeated after 3 wk rest	2/11	1/5	3/16	5/16 (31%)

*Each figure indicates the number of patients responsive among the total treated.

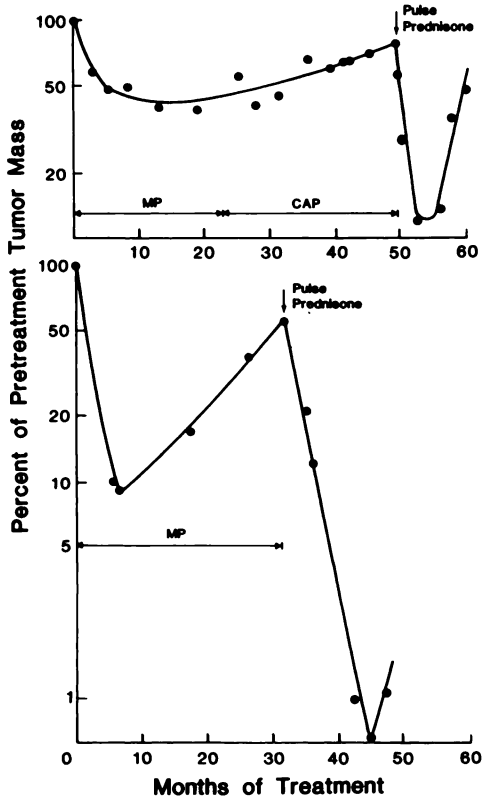

Fig. 2. Marked reductions in myeloma tumor mass from frequent prednisone pulses alone in two patients with progressive disease despite monthly melphalan-prednisone (MP) or cytoxan-doxorubicin-prednisone (CAP).

combinations that had included prior vincristine and doxorubicin.

Doxorubicin Plus Prednisone

As the occasional value of a frequent prednisone schedule was shown, 30 consecutive patients with resistant myeloma received a vincristine-doxorubicin-frequent prednisone combination (Table 3). Vincristine was used instead of vindesine in order to provide a higher doxorubicin dose without added myelosuppression and because vindesine alone had shown no clinical activity. Prednisone was given without the 3-wk interval between cycles, but in a slightly lower daily dose (45 mg/sq m/day) than when given alone or with vindesine. None had received prior pulse prednisone in either of the two previously described programs, or doxorubicin during the previous year, but all had confirmed resistance to vincristine-alkylating agent-prednisone combinations repeated monthly (e.g., vincristine-melphalan-cyclophosphamide-prednisone or vincristine-cyclophosphamide-prednisone). Of 30 treated patients, 7 reduced their myeloma tumor mass by at least 75% (23%), including 2 who had never responded to prior chemotherapy (Table 3). Seven

Table 3. Vincristine-Doxorubicin-Pulse Prednisone Treatment for Refractory Myeloma

Vincristine 1.5 mg i.v. day 1 + Doxorubicin 35 mg/sq m i.v. day 1 + Prednisone 45 mg/sq m/day × 5 days, repeated every 8 days × 3 pulses			Cycle repeated every 25 days
	Previously Unresponsive	Previously Relapsing	Total Response
>75% Tumor mass reduction	2/12	5/18	7/30 (23%)
>50% Tumor mass reduction	5/12	9/18	14/30 (47%)

additional patients reduced their serum myeloma protein by more than 50% and were considered "improved," so that the overall frequency of objective benefit was 47%. Figure 3 depicts serial tumor mass changes in 4 responsive patients.

Clinical Course

All 23 patients who responded or improved in this study achieved marked clinical benefit in terms of reduced pain, improved performance, rising hemoglobin, and reduction of bone marrow plasma cells. Forty-six patients with a hemoglobin level less than 12 g/dl received a prednisone pulse program for at least 2 mo. Of 18 anemic responders, 15 increased their hemoglobin by at least 1.7 g/dl, an elevation observed in only 1 of 28 anemic nonresponders ($p < 0.001$); the median hemoglobin increment in responders was 2.6 g/dl. Several bedridden patients developed an almost normal performance status. The median survival from the start of treatment was 16 mo for responders and 8 mo for nonresponders ($p < 0.01$); all responders lived at least 9 mo, by which time 62% of nonresponders had died (Fig. 4).

The remission time was calculated for each of the 23 patients with response or improvement from the interval between the onset of remission (50% myeloma protein reduction) and the first evidence of rising myeloma protein (or death in one patient who died of bronchogenic carcinoma). The median duration of tumor control was only 7 mo, a time much shorter than the 20 mo observed in previously untreated patients responding and improving to chemotherapy.[10] The median tumor halving time in our 23 responders was 1.8 mo (range 0.8–5 mo), a speed similar to that in previously untreated patients.[11] Tumor doubling times were short in all patients who relapsed after achieving remission; the median tumor doubling time was 1.6 mo in 12 relapsing patients with evaluable data, a speed similar to that of 2.0 mo in 40 consecutive patients relapsing to standard combinations.[10]

The clinical features of the 23 patients with response or improvement were compared with those of nonre-

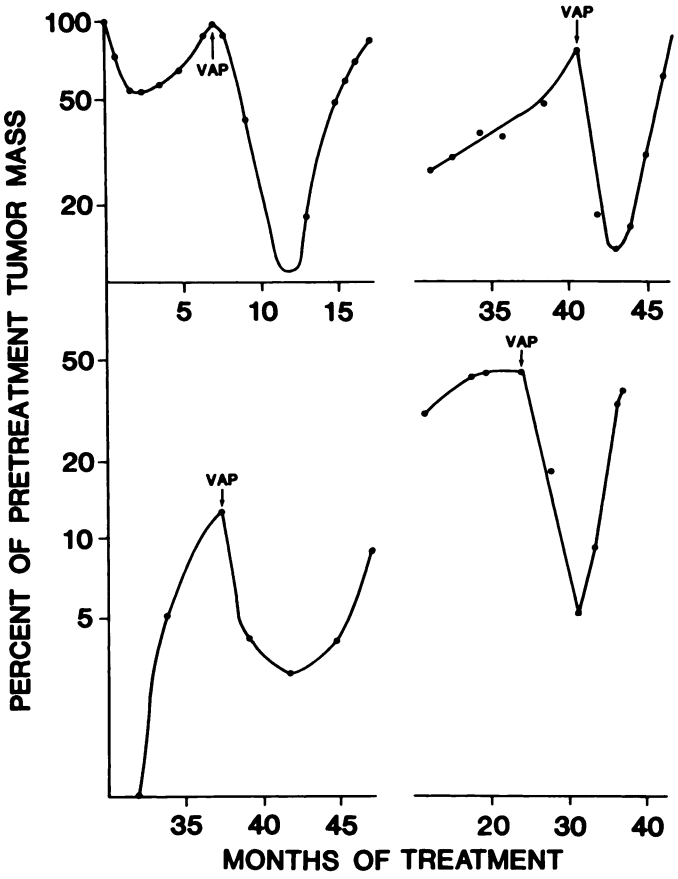

Fig. 3. Marked reductions in tumor mass from vincristine-doxorubicin-pulse prednisone (VAP) in four patients with progressive disease despite monthly courses of alkylating agents with prednisone. Remissions were short in all patients.

sponders in an attempt to identify any feature that might be associated with response. No abnormality, such as age, protein type, tumor mass grade, etc., was associated with the occurrence of remission, although none of the 8 patients with only Bence Jones protein responded. One-half of the 62 patients who received prednisone developed febrile episodes with temperature elevations to more than 101°F. All but two responded to appropriate antibiotic treatments, including 12 who required hospitalization. Two patients died from rapidly progressive bilateral pneumonia.

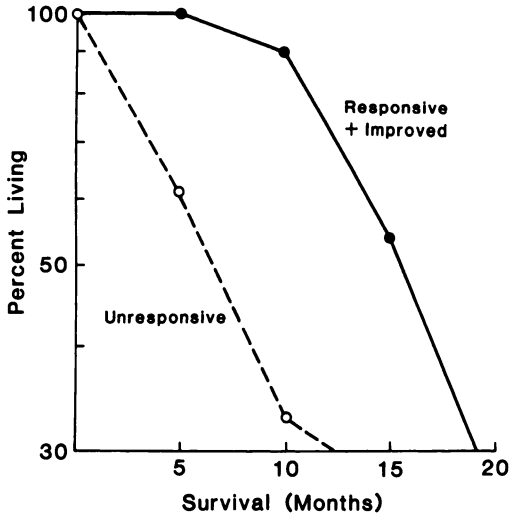

Fig. 4. Survival from onset of therapy for all 23 responders and 39 nonresponders to the 3 therapies with pulse prednisone. The difference was significant by Wilcoxon analysis ($p < 0.01$), and all responders lived at least 9 mo from the start of treatment.

DISCUSSION

Very few agents have been identified with clinical activity in myeloma patients resistant to intermittent melphalan-prednisone or similar drug combinations. In those studies that included at least 20 patients, about one-fourth benefitted from doxorubicin regimens for short durations. Thus, using response criteria based primarily on a 50% reduction of myeloma protein, Kyle et al. reported a 20% response rate from a BCNU-doxorubicin-prednisone combination;[1] Bonnet et al. found that 30% of relapsing patients achieved remission in contrast to only 7% of previously unresponsive patients.[2] The median duration of survival prolongation for responders was short in both studies, at 7 and 10 mo, respectively. Nitrosoureas, cyclophosphamide, hexamethylmelamine, and human leukocyte interferon have reduced tumor mass in occasional patients.[3-7] Thus, the first report by Houwen et al. that

frequent courses of vindesine-prednisone achieved remissions in 6 of 11 patients was promising,[8] although the response rate was only 25% after treatment of a larger number of patients.[9]

Our study confirmed the utility of a weekly program of vindesine-prednisone given in intermittent pulses, as described by Houwen et al.,[8,9] but indicated that the benefit resulted primarily from the frequent courses of large doses of prednisone. Using response criteria based on a 50% reduction of myeloma protein production, about one-fourth of our patients responded, regardless of whether they had received vindesine-prednisone or prednisone alone. No remissions were noted in a small number of patients treated with vindesine alone, but all had been refractory to prior regimens that had included vincristine. Furthermore, two of three patients responded to prednisone after prior resistance to vindesine, while none of five patients responded to vindesine after prior resistance to prednisone. While further trials of vindesine alone may be useful in patients not previously exposed to vinca alkaloids, significant activity seems unlikely in view of the ineffectiveness of vinblastine in patients with refractory myeloma[12] and the slight gain from vincristine in combination regimens for previously untreated patients.[10]

Responses resulted from frequent prednisone pulses, even though short 4-day courses had been included in previous alkylating agent–prednisone combinations repeated at monthly intervals. Thus, significant tumor sensitivity to prednisone existed in some patients who required a more intensive corticosteroid program than usually employed. We wondered whether more steroid receptors were present on the plasma cells of our responders in comparison with nonresponders. Until patients are better classified by corticosteroid receptor assays,[13] or by in vitro assessments of tumor sensitivity,[14] all patients with advanced refractory myeloma should receive a treatment program that includes frequent prednisone. This applies especially to patients with severe pancytopenia, or in whom chemotherapy must be delayed because of palliative radiotherapy. Such a dose regimen may be useful in some patients with other B-cell neoplasms, such as refractory lymphoma or chronic lymphocytic leukemia. Frequent self-monitoring by patients for possible infection during the 3-day rest between prednisone courses, and regular physician review of compliance, were useful in the detection and early antibiotic treatment of septic episodes.

Remission durations from pulse prednisone alone or in combination with vindesine or doxorubicin were usually short, but the quality of life during the remission period was excellent in comparison with the repeated disease morbidity until death in most nonresponders. Such short remissions to effective new drug combinations are common in refractory myeloma,[1-4] as well as in other malignancies, and accounted for modest survival prolongation. Perhaps more effective consolidation programs than the regimens used here, such as with cycle-active agents or large doses of purified interferon, might produce longer remission and survival times in future trials.

The addition of frequent prednisone courses to a vincristine-doxorubicin combination improved the results in refractory myeloma, in comparison with our previous trials using a standard vincristine-nitrosourea-doxorubicin-prednisone dose regimen (VBAP).[2] Thus, in contrast to the previous 7% response rate from monthly VBAP in nonresponders, 5 of 12 responded to a program that combined a higher and probably more effective doxorubicin dose with more frequent prednisone. Tumor reductions by 50% in 9 of 18 relapsing patients were also better than our previous 30% response rate in similar patients treated with VBAP ($p < 0.02$). Thus, a vincristine-high-dose doxorubicin-pulse prednisone program provided the best results achieved to date in our patients with refractory myeloma. This gain consisted mainly of an improved frequency of response, with no apparent improvement in the duration of response. In view of the rapidity of response, two cycles of treatment were usually sufficient to define myeloma protein changes adequately and to indicate the likelihood of remission; this approach should reduce the risk of infection from repeated exposures to prednisone. Of further interest was that prior exposure to doxorubicin or the presence of severe pancytopenia did not preclude a response to pulse prednisone treatment alone.

ACKNOWLEDGMENT

The authors are grateful to Kay Delasalle for assisting with the analysis.

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