EFFECTIVE TREATMENT OF ADVANCED MULTIPLE MYELOMA REFRACTORY TO ALKYLATING AGENTS

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Abstract Twenty-nine patients with advanced refractory multiple myeloma were treated with intermittent high-dose dexamethasone in combination with four-day infusions of vincristine and doxorubicin. Rapid and marked tumor-mass reduction (>75 per cent) was noted in 14 of 20 patients whose disease was resistant to alkylating agents and in 3 of 9 patients with additional resistance to doxorubicin — a result far superior to those in previous trials with similar patients. In responsive patients, remissions were of excellent quality, and survival was significantly longer than in unresponsive patients. (N Engl J Med 1984; 310:1353-6.)

THE prognosis of patients with multiple myeloma that is refractory to combinations of alkylating agents and prednisone has been poor because few effective salvage treatments are available.[1-3] In a recent study, a combination of vincristine, doxorubicin, and pulsed prednisone induced substantial reductions in tumor mass in about half the patients with advanced refractory disease.[4] More frequent courses of prednisone alone were also effective in patients who had been resistant to previous drug combinations that had included monthly prednisone, suggesting a dose-dependent antitumor effect from corticosteroids. These observations suggested that the results might be improved with even higher doses of corticosteroids combined with a continuous infusion of vinca alkaloid and doxorubicin to affect more slowly proliferating plasma cells. This report summarizes our experience with high doses of dexamethasone in conjunction with four-day infusions of vincristine and doxorubicin. Seventy per cent of patients with advanced myeloma that was refractory to alkylating agents had marked reductions in tumor mass — a result superior to any previously achieved in our patients with resistant myeloma.

METHODS

Between January and October 1983, 29 patients with advanced refractory multiple myeloma were treated with a combination of vincristine, doxorubicin (adriamycin), and dexamethasone (VAD). Their clinical features were similar to those described in previous large groups of patients with resistant myeloma.[1-4] The median age was 61 years, and 72 per cent of the patients had an intermediate or high tumor-mass stage. Twelve patients had IgG myeloma and 11 had IgA myeloma; 6 patients secreted Bence Jones protein only. Patients with nonsecretory myeloma were ineligible for the study because there was no myeloma-protein marker from which to evaluate a response. Previously unresponsive patients with a low and stable tumor mass were ineligible because they were asymptomatic and had a good prognosis.

The VAD regimen consisted of four-day continuous infusions of vincristine (0.4 mg per day) and doxorubicin (9 mg per square meter of body-surface area per day), given through an indwelling catheter with use of Travenol pumps; in addition, patients received dexamethasone in a dose of 40 mg each morning for four days, beginning on Days 1, 9, and 17 of each cycle. Treatment was usually initiated and continued in the outpatient clinic unless complications developed. Twenty patients were resistant to alkylating agent–prednisone combinations (VAD I), and the other nine patients were also resistant to prior doxorubicin combinations (e.g., monthly vincristine, cyclophosphamide, doxorubicin [adriamycin], and prednisone) (VAD II). In all patients, tumor resistance was present despite myelosuppressive doses of chemotherapy. No patient had been included in previous studies concerning the utility of therapy with vincristine, doxorubicin, and pulsed prednisone therapy.[4] There were 14 patients who had never responded to a median of 13 months of prior therapy (VAD I, seven patients; VAD II, seven patients). A second group of 15 patients had responded to prior treatment and had relapsed after a median duration of 36 months despite continued chemotherapy (VAD I, 13 patients; VAD II, 2 patients). Thus, all patients had obvious resistance to a long course of myelosuppressive chemotherapy, and tumor progression was evident in most patients.

All patients received prophylactic antacid treatment with cimetidine and antibiotic prophylaxis with trimethoprim–sulfamethoxazole. Special attention was given to the early detection of infection; all patients were asked to record evening temperatures and to seek medical evaluation promptly if temperatures exceeded 38°C.

All trials included weekly measurements of blood counts and monthly assessment of laboratory chemistry and electrophoretic data. Marrow aspirations were performed to assess the RNA content of plasma cells by flow cytometry and serial changes in the degree of plasma-cell infiltration.[5] A response was defined as a reduction in tumor mass exceeding 75 per cent, with disappearance of Bence Jones protein excretion.[6] Changes in tumor mass from the start of treatment were calculated from changes in myeloma-protein production; this assessment considered the serum myeloma-protein concentration, the change in IgG catabolic rate with falling levels, the estimated plasma volume, and the background of normal gamma globulin. Four patients died during the first two months of therapy, and their treatments were considered failures.

VAD chemotherapy was repeated until a maximum reduction in myeloma protein had occurred. Responsive patients in whom serum myeloma protein had disappeared or levels had stabilized received four additional courses of VAD before treatment was stopped. Survival was calculated by life-table analysis from the onset of VAD treatment until death.

RESULTS

Twenty-nine consecutive patients with resistant myeloma received the VAD regimen. One group of 20 patients who were resistant to melphalan–prednisone included 7 patients who had received doxorubicin at least six months earlier (VAD I). Reductions in tumor mass exceeding 75 per cent were observed in 14 patients in this group (70 per cent) (Table 1); this response rate was significantly higher than the 23 per cent frequency of 75 per cent tumor reduction observed in comparable previous patients treated with vincristine, doxorubicin (adriamycin), and pulsed prednisone (VAP) ($P<0.05$).[4] The tumor reduction occurred rapidly; the median tumor-halving time

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Table 1. Response to VAD Therapy According to Effects of Earlier Treatment.

Patient Group	Responding Patients *		
	Previously Unresponsive	Previously Relapsing	Total
Resistant to melphalan (VAD I)	3 of 7	11 of 13	14 of 20 (70%)
Resistant to melphalan and doxorubicin (VAD II)	3 of 7	0 of 2	3 of 9 (33%)
Total	6 of 14	11 of 15	17 of 29 (59%)

*A response was defined as a >75 per cent reduction in tumor mass. Among the responding patients, tumor halving occurred in a median of 0.9 month (range, 0.3 to 1.6).

pearance of the abnormal globulin from the electrophoretic strip occurred in two patients, as compared with none of the patients treated with VAP. Among six patients with Bence Jones protein only, light-chain excretion disappeared in two, as compared with none of eight similar patients treated with VAP.[4] In the second group, containing nine patients who had been resistant to both melphalan and doxorubicin combinations (VAD II), only three patients responded (Table 1); such patients had not been eligible for the earlier VAP program. Among the patients who had initially responded to previous treatment and then relapsed, 73 per cent responded to VAD, as compared with 43 per cent of those who had been unresponsive to prior therapy ($P = 0.16$). All six patients in this latter group were clearly resistant in that they had either progressive disease (three patients) or a stable tumor mass despite at least six months of prior therapy (three patients). As in previous studies, a high RNA index (ratio of mean RNA content of marrow plasma cells vs. that of normal lymphocytes[5]) was associated with a high response rate. Thus, there was a progressive increase in response rate, from 0 per cent in patients with a low RNA index (<4) to 50 per cent in those with intermediate values (4 to 6) and 87 per cent in those with a high RNA index (>6) ($P<0.01$) (Fig. 1).

Clinical Course

All 17 responding patients also had marked clinical benefit, with reduced pain and improved performance. In 15 of the 29 patients, the pretreatment hemoglobin concentration was <10 g per deciliter. In six of nine anemic responders the hemoglobin rose by at least 2.5 g per deciliter, to more than 11.5 g per deciliter during remission, with chronic renal failure accounting for the exceptions. None of the six anemic nonresponders had any rise in hemoglobin level.

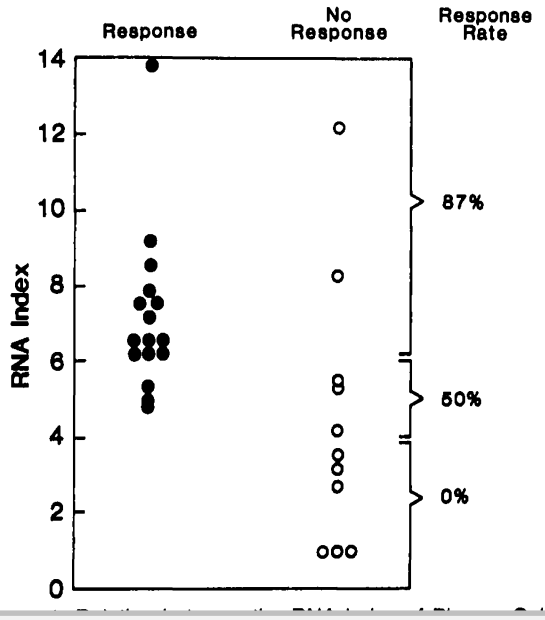
Myeloma-protein reduction was accompanied by a similarly rapid and marked clearing of bone-marrow plasmacytosis, from a pretreatment median of 38 per cent to a median of 1 per cent within one month (Fig. 2). The survival of responding patients was significantly longer than that of patients in whom treatment

dian survival time of all patients was short, the median relapse-free survival time has not been reached. There were two patients who had relapsed four and six months, respectively, after completion of VAD therapy, who again had a prompt >75 per cent reduction in tumor mass upon reinitiation of VAD.

VAD chemotherapy induced mild and reversible depressions of blood counts. During the first two courses, the median nadir of granulocytes was 1700 per microliter (range, 250 to 4100), and that of platelets was 138,000 per microliter (range, 11,000 to 233,000). As in previous studies with pulsed prednisone, infection represented the most important complication. Eleven patients had episodes of fever, requiring hospitalization in nine, and an infectious agent was identified in eight patients. There were four cases of pneumonia, two episodes of gram-positive bacteremia (probably related to the indwelling catheter), and two cases of gram-negative sepsis. Four patients had documented viral infections, including herpetic esophagitis (two patients), herpes zoster infection (one patient), and cytomegalovirus infection with hepatitis (one patient). The herpetic infections responded promptly to treatment with acyclovir and did not require interruption of VAD therapy. Perhaps because of the regular use of cimetidine, gastrointestinal side effects were minimal. A paralytic ileus developed in one patient but did not recur after omission of vincristine from the VAD regimen. Severe depression developed in another patient but was managed successfully with antidepressants, so that dexamethasone treatment could be continued.

Discussion

The VAD regimen was developed as a result of our previous findings that the addition of frequent



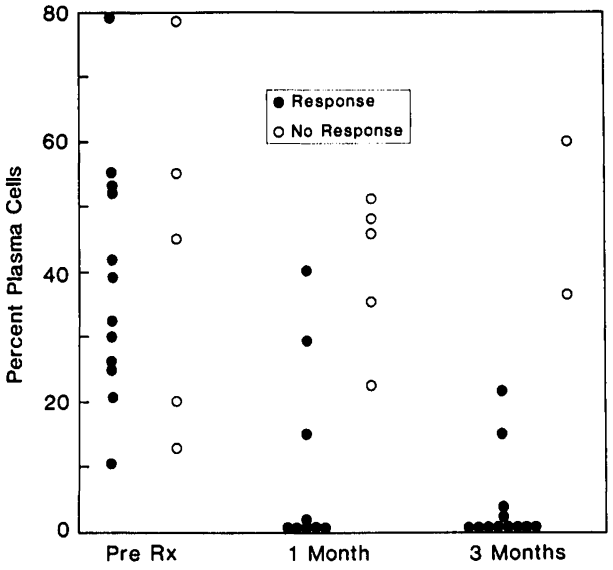


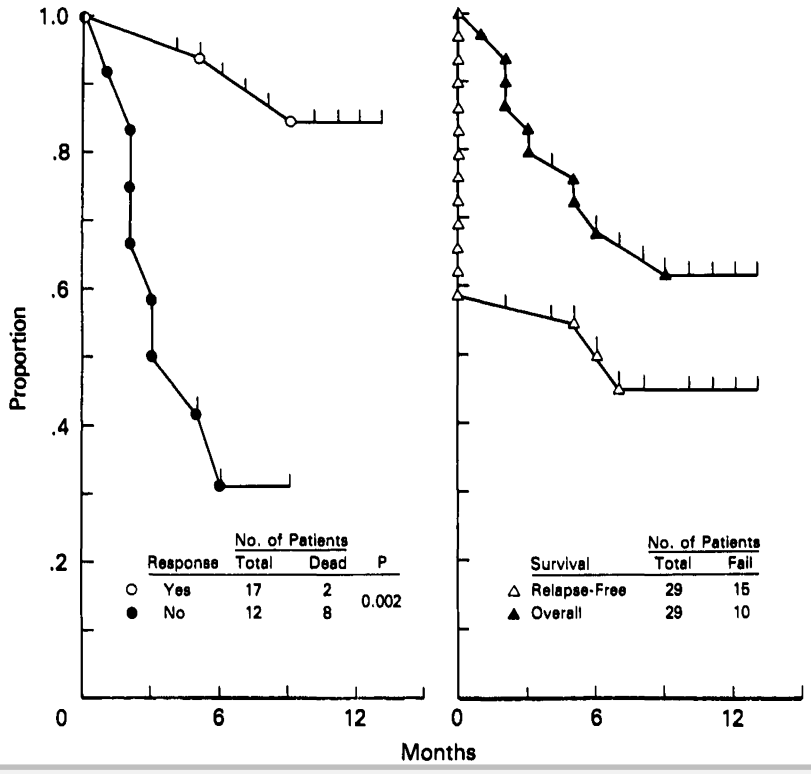
Figure 2. Proportions of Bone-Marrow Plasma Cells Determined by Flow Cytometry before and after VAD Therapy in Responsive and Unresponsive Patients.

prednisone pulses increased the response rate among patients with resistant myeloma.[4] Thus, a sixfold higher dose of steroid equivalent in the form of dexamethasone was combined with continuous infusion of vincristine and doxorubicin. The rationale for the protracted administration of vincristine and doxorubicin was based on the long generation time and low growth fraction of plasma cells in most patients.[7] Indeed, a greater reduction of myeloma cells grown in tissue culture has been reported after prolonged as opposed to brief exposures to vincristine.[8] Since vincristine has a serum-half life of less than 30 minutes after administration as a bolus, a prolonged infusion seemed more appropriate.[9] In addition to exerting a possibly superior antitumor effect, a continuous infusion of doxorubicin would also reduce the risk of cardiomyopathy associated with repeated injections as a bolus and would therefore permit a longer use of the drug in responding patients.

In patients who were resistant to alkylating agent–corticosteroid combinations, VAD treatment induced a higher frequency of substantial tumor reduction in a more rapid manner than observed with any previous program, either for

sponses occurred in about 70 per cent of patients who were resistant to melphalan, as compared with about 25 per cent of patients treated with VAP. The marked sensitivity of plasma cells was also demonstrated by the prompt and marked decrease in bone-marrow plasmacytosis, indicating that reductions in myeloma protein resulted from a true tumoricidal effect. Since all responses were evident after only one course, the toxicity could be minimized in patients who were unlikely to benefit from this treatment, who should be offered other investigational therapies. In addition, unresponsive patients had a significantly lower RNA content in their plasma cells than did responsive patients. Confirming the important prognostic role of plasma cell RNA content in regard to induction of remission, this assessment identified patients who were most likely to benefit from this treatment program.[5]

The superior results achieved with VAD as compared with VAP resulted from one or both of the two major alterations in the treatment regimen: dexamethasone was provided in a higher steroid dose, and a prolonged vincristine–doxorubicin dose regimen was given; this regimen may have been more effective against slowly cycling plasma cells. The important therapeutic role of dexamethasone was also supported by the observed responses in 4 of 10 other melphalan-resistant patients who were receiving this steroid alone (not included in the present series) and in a similar proportion of doxorubicin-resistant patients who were receiving VAD (VAD II). These observa-



tions suggest that patients who are resistant to doxorubicin are more likely to be resistant to corticosteroids. Such steroid therapy seems appropriate for patients with pancytopenia from extensive bone-marrow infiltration by plasma cells and for those receiving palliative radiotherapy when myelosuppressive chemotherapy must be delayed.

The major toxic effect of VAD was infection, which was attributed in part to the intensive steroid program — a complication noted previously with pulsed prednisone therapy. Combined with frequent self-monitoring for fever, longer periods without any steroid therapy might allow earlier recognition of sepsis and recovery from immunosuppression. Less frequent infection has resulted from our current program, which omits the second and third dexamethasone pulses in every second course of VAD. Finally, previously untreated patients may benefit from alternating two therapeutic combinations that are unlikely to lead to cross-resistance — namely, VAD and melphalan–prednisone — in an effort to reduce the emergence of drug-resistant tumor clones.[10] Such an approach has been successful with alternating combinations of mechlorethamine–vincristine–procarbazine–prednisone and doxorubicin–bleomycin–vinblastine–dacarbazine in the treatment of Hodgkin's disease.[11] It is also supported by our experience with three consecutive patients receiving VAD who had further myeloma-protein reductions after a stable response was achieved with standard vincristine–cyclophosphamide–doxorubicin–prednisone induction treatment.

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