

Chemotherapy for Multiple Myeloma

RAYMOND ALEXANIAN, MD, AND ROBERT DREICER, MD

The effects of eight different drug combinations were evaluated in 256 patients with multiple myeloma. The response rate and time to remission were superior from regimens that added both vincristine and Adriamycin (doxorubicin) to an alkylating agent-prednisone combination. There was no improvement in response rate or survival time from two alternating drug combinations evaluated in an attempt to achieve more marked tumor reductions and to delay the emergence of resistant subclones. The addition of levamisole during remission maintenance did not improve survival time. Results supported the utility of unmaintained remission follow-up in selected patients with marked reductions in myeloma cell mass.

Cancer 53:583-588, 1984

SINCE the development of intermittent melphalan-prednisone treatment for multiple myeloma about 15 years ago, there has been limited progress in controlling this disease. Combinations of different alkylating agents have not improved results in most studies,^{1,2} whereas the addition of vincristine and Adriamycin (doxorubicin) has contributed only slight gains.¹ Thus, a combination of vincristine-Adriamycin-prednisone with either cyclophosphamide (VCAP) or a nitrosourea (VBAP) increased the response rate to about 60% and the median survival time to about 30 months.¹ Alternating or sequential drug combinations have been useful in Hodgkin's disease and metastatic breast cancer,^{3,4} perhaps by delaying the evolution of resistant tumor subclones. This study evaluated the utility of two alternating schedules of most drugs considered active in myeloma, as well as evaluating whether levamisole might improve the longevity of responding patients. The role of unmaintained remission follow-up and the value of certain prognostic factors in predicting survival time were also evaluated.

Methods

This report presents an analysis of 142 consecutive patients with multiple myeloma whose treatment began between February 1977 and November 1980. Only patients previously untreated for myeloma were included in the study. The diagnosis was based on standard criteria that included bone marrow plasmacytosis exceeding 15%, and monoclonal globulin peaks in symptomatic patients; all patients with low myeloma globulin peaks on serum

electrophoresis (<4.0 g/dl) were also symptomatic, and showed multiple lytic bone lesions and depression of normal immunoglobulins. The pretreatment tumor mass was rated as high, intermediate, or low, in accordance with a clinical staging system described previously.^{5,6}

Treatment Regimens

Between February 1977 and July 1979, 106 patients were assigned at random to one of three different drug combinations (Tables 1 and 2). These regimens consisted of vincristine-melphalan-cyclophosphamide-prednisone alternating with vincristine-cyclophosphamide-Adriamycin-prednisone (VMCP/VCAP), three courses of VMCP followed by three courses of vincristine-bischothyl-nitrosourea (BCNU)-Adriamycin-prednisone (VMCP/VBAP), or melphalan-prednisone (MP). Between July 1979 and November 1980, 36 additional patients were assigned at random to one of two different combinations that consisted of either the VMCP/VBAP sequential program or vincristine-cyclophosphamide-prednisone (VCP) (Tables 1 and 2); 50% of these patients also received levamisole (50 mg four times daily on days 8, 9, 15, and 16 of each cycle), but in the absence of any obvious effect of levamisole on response rate, these patients were grouped to evaluate their response to either VMCP/VBAP or VCP. All drug combinations were repeated at 25-day intervals, provided there was recovery of granulocytes to more than $1800/\text{mm}^3$ and of platelets to more than $100,000/\text{mm}^3$.

These treatments were given in initial doses outlined in Table 2, and adjusted to produce moderate bone marrow toxicity, *i.e.*, nadir in granulocytes between 1000 to $2000/\text{mm}^3$, or in platelets between $40,000$ to $80,000/\text{mm}^3$. Clinical response was based on criteria described previously that required a 75% reduction of myeloma protein production and/or disappearance of Bence Jones protein

From The University of Texas M.D. Anderson Hospital and Tumor Institute, Houston, Texas.

Address for reprint: Raymond Alexanian, MD, M. D. Anderson Hospital, Houston, Texas 77030.

The authors thank Kay Delasalle and Dr. Dennis Dixon for many portions of this analysis.

Accepted for publication January 1, 1983.

TABLE 1. Response Rates in Multiple Myeloma

	No. treated	No. responsive	Response rate (%)
Previous study			
1974-1977			
CAP	22	10	45
VCAP	35	22	63
VMCP with early VCAP to nonresponders	34	18	53
VBAP	23	14	61
Current study			
1977-1979			
VMCP/VCAP (alternating)	42	23	55
VMCP $\times$ 3/VBAP $\times$ 3 (sequential)	34	20	60
MP	30	16	53
1979-1980			
VMCP $\times$ 3/VBAP $\times$ 3	22	14	64
VCP	14	2	14

CAP: cyclophosphamide-Adriamycin-prednisone; VCAP: vincristine-cyclophosphamide-Adriamycin-prednisone; VMCP: vincristine-melphalan-cyclophosphamide-prednisone; VCP: vincristine-cyclophosphamide-prednisone; VBAP: vincristine-bischloroethyl-nitrosourea (BCNU)-Adriamycin-prednisone.

after the electrophoresis of urine concentrates.^{1,6} All patients who did not achieve such marked reductions of tumor mass were rated as failures to treatment, including patients with early deaths within 4 weeks. Serial calculations of myeloma protein production by computer program considered the serum myeloma protein concentration, the changing IgG catabolic rate, the estimated plasma volume, and the background of normal gamma globulin.⁷ The speed of tumor reduction was also compared for each treatment in all patients with IgG or IgA myeloma protein peaks.

TABLE 2. Chemotherapy Dose Regimens

VMCP	Vincristine 1 mg IV d 1 Melphalan 5 mg/m ² /d $\times$ 4 d Cyclophosphamide 100 mg/m ² /d $\times$ 4 d Prednisone 100 mg/d $\times$ 4 d
VCAP	Vincristine 1 mg IV d 1 Cyclophosphamide 100 mg/m ² /d $\times$ 4 d Adriamycin 25 mg/m ² IV d 1 Prednisone 100 mg/d $\times$ 4 d
CAP	Cyclophosphamide 100 mg/m ² /d $\times$ 4 d Adriamycin 25 mg/m ² IV d 1 Prednisone 100 mg/d $\times$ 4 d
VBAP	Vincristine 1 mg IV d 1 BCNU 25 mg/m ² IV d 1 Adriamycin 25 mg/m ² IV d 1 Prednisone 100 mg/d $\times$ 4 d
MP	Melphalan 7 mg/m ² /d $\times$ 4 d Prednisone 100 mg/d $\times$ 4 d
VCP	Vincristine 1 mg IV d 1 Cyclophosphamide 130 mg/m ² /d $\times$ 4 d Prednisone 100 mg/d $\times$ 4 d

Remission Maintenance

Between August 1977 and October 1980, 57 eligible responding patients who had received at least 6 months of drug treatment on any of the three initial induction regimens were assigned at random to one of two chemoinmunotherapy maintenance programs (Table 3). These programs consisted of 12 months of either VMCP or VMCP with levamisole as described above. Maintenance treatment continued for 12 months on both programs, after which no chemotherapy was given, until relapse, to those in whom myeloma proteins had disappeared (Table 3). When relapse developed, the VMCP combination was reinstituted and continued until the patient relapsed or died. The frequency and duration of a second reduction in tumor mass were defined in 24 patients relapsing from unmaintained remissions in this and a previous study after they had completed 1 year of a VMCP-BCG (bacille Calmette Guérin) maintenance program.⁸

Previous Study

Response and survival data were compared with those from an immediately preceding study conducted from 1974 to 1977, in which 114 patients were randomized among four induction treatments (Tables 1 and 2). These treatments consisted of identical regimens of VCAP, VMCP followed by VCAP to all nonresponders after 6 months, VBAP, and cyclophosphamide-Adriamycin-prednisone (CAP). Patients responding to any of these treatments received a 12-month consolidation program using alternating VMCP-BCG as described previously⁸ (Table 3). All patients were included in survival calculations that used the life-table method from the start of both initial and maintenance chemotherapy until death.⁹

Results

Comparability of Treatment Groups

The frequency and severity of specific disease complications were evaluated in each group of patients receiving the different induction and maintenance treatments. There were no major differences in those characteristics known to affect prognosis, such as tumor mass grade, anemia, hypercalcemia, or renal failure. Slightly more patients with poor prognostic features for survival were treated initially with alternating VMCP/VCAP, and more patients with good prognostic features received initial MP.

Frequency of Response

Between February 1977 and July 1979, 106 patients received one of three different drug combinations, *i.e.*, VMCP/VCAP, VMCP/VBAP or MP. The 2% of patients

TABLE 3. Treatment Schema

Randomization for induction treatment (6 mo)	Responding patients		
	Maintenance treatment (12 mo)	Peak disappearance	Peak persistence
Previous study (1974-1977) CAP VCAP VMCP VBAP	VMCP + BCG	No treatment	No treatment
Current study (1977-1980) VMCP/VCAP VMCP/VBAP MP	VMCP vs VMCP + levamisole	No treatment	VMCP

CAP: cyclophosphamide-Adriamycin-prednisone; VCAP: vincristine-cyclophosphamide-Adriamycin-prednisone; VMCP: vincristine-melphalan-cyclophosphamide-prednisone; BCG: bacille Calmette Guérin;

VBAP: vincristine-bischloroethyl-nitrosourea (BCNU)-Adriamycin-prednisone; MP: melphalan-prednisone.

not evaluable because of early death within 4 weeks were rated as failures. Response results were compared with those of 114 comparable patients who received one of four treatments given in the immediately preceding study, *i.e.*, CAP, VCAP, VMCP, or VBAP. Six of the seven treatments produced a similar frequency of remission, between 53% and 63%; the exception was the 45% response rate from CAP given between 1974 and 1977 (Table 1). For the 36 patients treated between 1979 and 1980, the response rate from VMCP/VBAP (64%) was similar to the identical program given previously from 1977 to 1979 (60%), but only 2 of 14 patients responded to VCP; 4 of 8 patients unresponsive to VCP achieved remissions from a later Adriamycin-prednisone combination. All patients were then evaluated according to whether both vincristine and Adriamycin had been given or whether one or both of these drugs had been omitted from the combination, *i.e.*, MP, VCP, or CAP. The response rate from the more complex combinations (58%) was 16% higher than that from those combinations without both vincristine and Adriamycin (42%) ($P = 0.03$) (Table 4).

Kinetics of Response

The speed of tumor mass change was evaluated from changes in serum myeloma protein production rate in all 205 patients with IgG or IgA serum peaks. Calculations were based on serial measurements of myeloma protein level, the changing IgG catabolic rate with changing serum concentration, and estimates of plasma volume from the hematocrit and weight as described previously.^{1,6,7} Post-treatment values were expressed as a percentage of the pretreatment myeloma protein production considered at 100%. Results from the 151 patients with serum peaks receiving vincristine-Adriamycin-alkylating agent-prednisone combinations were compared with those from the 54 patients who had not received added vincristine-Adriamycin. More rapid tumor reductions occurred in patients who received the more complex regimens, in whom the median serum myeloma protein halving time was 3.9 months for all patients and 1.5 months for responding patients. (Those patients who did not reduce serum myeloma protein by 50% were considered to have an infinite halving time). In contrast, the median halving time was

TABLE 4. Response Rates From Various Chemotherapy Combinations

	No. treated	No. responsive	Response rate (%)
Includes both vincristine + Adriamycin VCAP VMCP + early VCAP to nonresponders VBAP VMCP/VCAP VMCP × 3/VBAP × 3	190	111	58
Excludes vincristine or Adriamycin MP VCP CAP	66	28	42

$P = 0.03$

VCAP: vincristine-cyclophosphamide-Adriamycin-prednisone; VMCP: vincristine-melphalan-cyclophosphamide-prednisone; VBAP: vincristine-bischloroethyl-nitrosourea (BCNU)-Adriamycin-predni-

sone; MP: melphalan-prednisone; VCP: vincristine-cyclophosphamide-prednisone; CAP: cyclophosphamide-Adriamycin-prednisone.

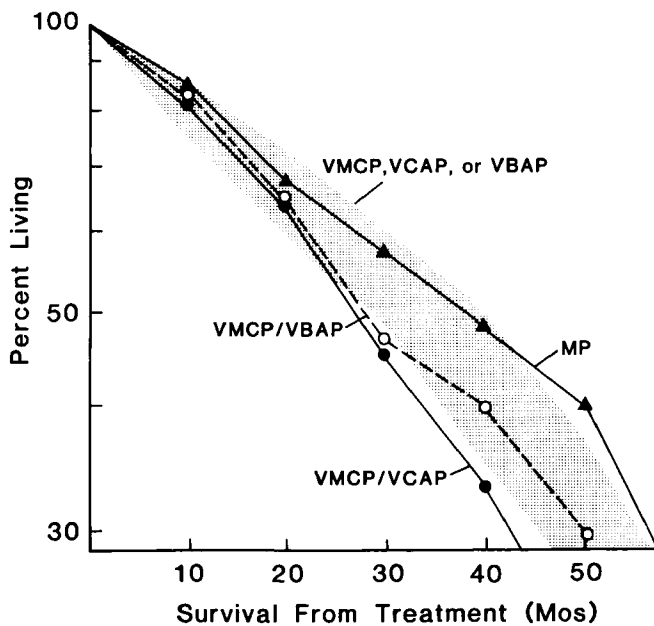


FIG. 1. Survival curves for the 106 patients treated with alternating VMCP/VCAP, VMCP/VBAP, or MP between 1977-1979, compared with those of patients treated with separate drug combinations (VMCP, VCAP, or VBAP) that fell within the shaded area. Favorable prognostic features for survival were most common among patients treated with MP, and least common among those receiving VMCP/VCAP.

8.3 months for all patients, and 2.0 months for the lower fraction of responding patients who had not received both vincristine and Adriamycin.

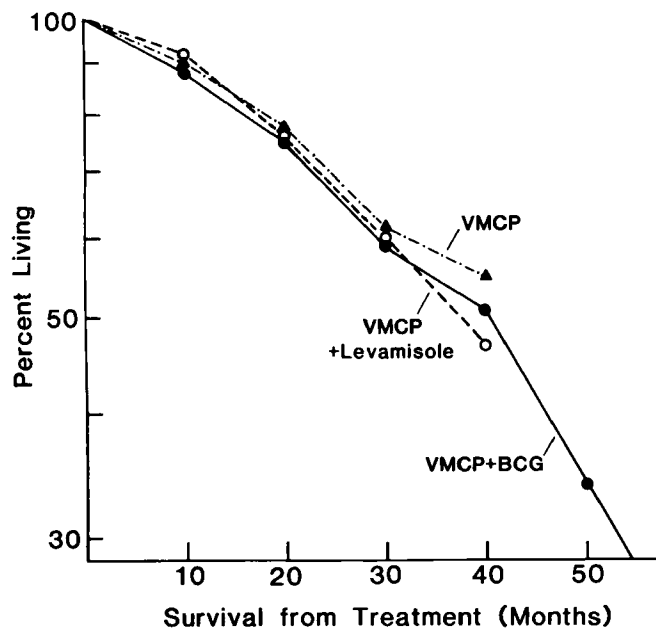


FIG. 2. The similar survival curves of 57 responding patients after randomization to either VMCP or VMCP + levamisole, compared with those of 59 responding patients receiving VMCP + BCG. None of the differences were significant ($P > 0.4$).

Survival Time

Survival was calculated for all patients receiving each of the induction therapies; longevity was similar for all treatments, the median survival ranging from 27 to 38 months. The median survival was almost identical at 30 months for the 190 patients in whom vincristine and Adriamycin were part of the early treatment program and 29 months for the 66 patients in whom one or both of these drugs had been omitted. Most of the latter also received multiple courses of VBAP or VCAP for refractory disease later in their treatment courses. No significant differences in survival were apparent among the 42 patients who received the VMCP/VCAP alternating program, the 34 patients given the VMCP/VBAP sequential combination, the 30 patients treated with MP between 1977 and 1979 and the 92 patients who received single combinations of either VCAP, VBAP, or VMCP between 1974 and 1977 ($P > 0.2$) (Fig. 1). The slightly longer survival of patients treated with MP was attributed to their higher frequency of favorable prognostic features and the use of later vincristine-Adriamycin combinations in most of this group when tumor resistance was apparent.

Remission Maintenance

Survival durations were compared for responding patients after random allocations to 1 year of treatment with either intermittent VMCP therapy or intermittent VMCP with added levamisole. All 57 patients were in remission at the time of randomization, which was no sooner than 6 months after the start of induction therapy. Results were compared with those from 59 responding patients in the immediately preceding study who were maintained for 1 year on the VMCP-BCG combination (Table 3).⁸ All three patient groups were comparable in terms of those major factors known to affect prognosis. As indicated in Figure 2, the survival from randomization for the VMCP-levamisole group was identical to that for patients receiving VMCP alone and for patients receiving the VMCP-BCG combination ($P > 0.4$). These survival curves were also similar to those found previously in comparable responding patients maintained on either azathioprine-prednisone, melphalan-cyclophosphamide-BCNU-prednisone (MCBP), or on no treatment until relapse.^{1,10}

The frequency of further decline in serum myeloma protein, with or without levamisole, was evaluated in responding patients with serum peaks greater than 1.0 g/100 ml and treated for at least 6 months. From calculations of serial tumor mass change, 53% of those receiving levamisole continued to reduce plasma cell mass further by more than 50%, in comparison with 44% of those not receiving levamisole ($P > 0.4$).

Unmaintained Remission

Of the 116 responding patients who received either the VMCP, VMCP + levamisole, or VMCP-BCG maintenance programs for 12 months, myeloma proteins had disappeared in 34 patients who were then followed without chemotherapy. The median duration of unmaintained remission was 14 months, with no differences between those who had presented with IgG, IgA, or only Bence Jones proteins. The resumption of VMCP with relapse of myeloma proteins reduced myeloma tumor mass by more than 50% in 12 of 24 patients treated to date (50%); these patients then had a median second maintained remission duration of 20 months. The median survival for all patients from follow-up without chemotherapy was 34 months, with a total median survival of 54 months from their first chemotherapy. Four relapsing and re-treated patients achieved second disappearances of their myeloma protein and then completed 18 months of a second VMCP consolidation program; these patients were then followed again without chemotherapy and had a second median unmaintained remission of only 4 months, in comparison with a median of 21 months for their first unmaintained remission ($P = 0.07$).

Prognostic Factors

The effects of a variety of clinical and laboratory features on the response to treatment and on survival time were evaluated; these included the pretreatment tumor mass grade, age, renal function, myeloma protein type, and 20 other factors commonly evaluated in patients with multiple myeloma. To control the role of treatment, only the 190 patients who received the superior drug combinations that included both vincristine and Adriamycin between 1974 and 1980 were included.

As in previous studies, no clinical feature was identified that predicted the occurrence of remission. The most important factors associated with shortening of survival were tumor mass load ($P = 0.003$), blood urea nitrogen levels greater than 30 mg/100 ml ($P = 0.008$), serum albumin levels less than 3.5 g/100 ml ($P = 0.011$), calcium levels greater than 11.5 mg/100 ml ($P = 0.012$), and hemoglobin less than 8.5 g/100 ml ($P = 0.028$). When all features were evaluated simultaneously by a multiple regression analysis based on the Cox model, only pretreatment tumor mass and hypoalbuminemia remained as significant variables. This analysis demonstrated the major role of tumor mass as a prognostic factor, presumably because it was either defined by or associated with most of the harmful clinical features.

Discussion

This report summarizes the results from eight different drug combinations in patients with multiple myeloma

treated over a 6-year period. All patients had unequivocal criteria for the diagnosis, and received intermittent courses of chemotherapy in maximal doses in a consistent manner. Despite the small number of patients in each group treated over different time periods, all groups appeared comparable, with a similar frequency and severity of those complications known to affect prognosis.⁶ Response to therapy was based on a 75% reduction of tumor mass as defined by a 75% reduction of serum myeloma protein production, and the elimination of Bence Jones protein, as described previously.^{1,11}

Those regimens that included both vincristine and Adriamycin early in the treatment program produced remissions in 16% more patients than other regimens given to comparable randomized patients. This result confirmed the superiority of the VCAP combination to the CAP combination reported previously,¹ was consistent with the 30% response rate from VBAP in patients relapsing after prior MP,¹² and was supported by the marked tumor reductions from an Adriamycin program in some of our unresponsive patients resistant to cyclophosphamide. In addition, combinations of vincristine-Adriamycin with alkylating agent-prednisone produced a more rapid reduction of serum myeloma protein as an index of tumor mass change. Thus, nonresponders were recognized earlier and other investigational therapies introduced sooner, especially when poor prognostic features were present. The similar survival times for all treatment groups were attributed to the use of vincristine-Adriamycin-prednisone combinations in 50% of our resistant patients not exposed previously to one or more of these drugs, many of whom either responded to treatment or had stable disease for many months. Thus, older treatments, such as MP, appeared inferior to more complex combinations, such as VCAP, in terms of the frequency and onset of remission.

Alternating drug combinations were evaluated to determine whether different drugs might be effective against different tumor subclones from the start of treatment, and whether neoplastic plasma cells resistant to some drugs might be sensitive to others.^{3,4} Also, we hoped that different drug combinations might reduce the spontaneous mutation rate of new subclones and thus delay the appearance of resistant cells.¹³ The response rates and survival for either the alternating VMCP/VCAP or the sequential VMCP/VBAP combinations were similar to those found previously in comparable patients treated with either VCAP or VBAP as a single combination, showing no clear gain from alternating the two regimens. We attributed this result to the similarity of most of the drugs used in our two alternating regimens. This finding suggests that more marked differences between drug combinations are necessary to improve the therapeutic results.

No improvement in survival and no further reduction

of residual cell mass was found when levamisole was added to the VMCP consolidation treatment in responding patients in an attempt to enhance patient immunity. Levamisole is an antihelminthic drug that improves some aspects of depressed immunity in man,^{14,15} prolongs remission after control of murine leukemia,¹⁶ and improves the depressed immunity of mice with myeloma.¹⁷ Survival times from either the VMCP or VMCP-levamisole treatments were similar to those of patients previously treated with VMCP-BCG and other maintenance programs. These findings did not indicate any useful role for levamisole in the maintenance treatment of responding patients with multiple myeloma.

We found a median unmaintained remission time of 14 months for the 30% of responding patients in whom myeloma proteins had disappeared. Follow-up under close supervision without additional treatment seems logical for patients who achieve such marked tumor reductions and are likely to enjoy prolonged clinical stability. This approach is in contrast to the continued chemotherapy necessary for most patients with persistent myeloma proteins, in whom the median unmaintained remission was only 6 months.⁸ Approximately 20% of those patients also had stable myeloma proteins and an unmaintained remission longer than 12 months; most of those patients had either presented with a low tumor mass at diagnosis and/or had a very slow onset of remission.

The lower frequency of a second remission with resumption of chemotherapy, along with the less marked degree and shorter duration of tumor reduction,¹⁰ indicated a gradual accumulation of drug-resistant cells during the no-treatment period. Whether the growth of such resistant cells was delayed in patients not receiving chemotherapy, in comparison with those maintained on treatment, could not be determined. More effective consolidation treatments that might reduce tumor burden further or delay the emergence of resistant clones and better patient selection from prognostic factor studies may permit more patients to be followed without chemotherapy. This approach is justified by the frequency of second (and sometimes third) remissions, the stable tumor load in most other patients after retreatment, the consequent long survival time of good quality, and the po-

tential for a lower frequency of therapy-induced leukemia.¹⁸

REFERENCES

1. Alexanian R, Salmon S, Bonnet J, Gehan E, Haut A, Weick J. Combination therapy for multiple myeloma. *Cancer* 1977; 40:2756-2771.
2. Bergsagel DE, Bailey AJ, Langley GR, Macdonald RN, White DF, Miller MB. The chemotherapy of plasma cell myeloma and the incidence of acute leukemia. *N Engl J Med* 1979; 301:743-748.
3. Bonnadona G, Zucali R, Monfardini S, Delena M, Uslenghi C. Combination chemotherapy of Hodgkin's disease with Adriamycin, bleomycin, vinblastine and imidazole carboxamide versus MOPP. *Cancer* 1975; 36:252-259.
4. Blumenschein G, Hortobagyi GN, Richman SP *et al.* Alternating noncross-resistant combination chemotherapy and active nonspecific immunotherapy for advanced breast carcinoma. *Cancer* 1980; 45:742-749.
5. Durie B, Salmon S. A clinical staging system for multiple myeloma. *Cancer* 1975; 36:842-854.
6. Alexanian R, Balcerzak S, Bonnet J *et al.* Prognostic factors in multiple myeloma. *Cancer* 1975; 36:1192-1201.
7. Salmon S, Wampler SB. Multiple myeloma: Quantitative staging and assessment of response with a programmable pocket calculator. *Blood* 1977; 49:379-389.
8. Alexanian R, Salmon S, Gutterman J, Bonnet J, Dixon D, Haut A. Chemoimmunotherapy for multiple myeloma. *Cancer* 1981; 47:1923-1929.
9. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 53:457-482.
10. Alexanian R, Gehan E, Haut A, Saiki J, Weick J. Unmaintained remissions in multiple myeloma. *Blood* 1978; 51:1005-1011.
11. McLaughlin P, Alexanian R. Myeloma protein kinetics following chemotherapy. *Blood* 1982; 60:851-855.
12. Bonnet J, Alexanian R, Salmon S, Bottomley R, Amare M, Haut A, Dixon D. Vincristine-BCNU-Adriamycin-prednisone (VBAP) combination in the treatment of relapsing or resistant multiple myeloma. *Cancer Treat Rep* 1982; 66:1267-1271.
13. Goldie JH, Coldman AJ. A mathematic model for relating the drug sensitivity of tumor to their spontaneous mutation rate. *Cancer Treat Rep* 1979; 63:1727-1733.
14. Ramot B, Biniaminov M, Shoham C, Rosenthal E. Effect of levamisole on E-rosette-forming cells *in vivo* and *in vitro* in Hodgkin's disease. *N Engl J Med* 1976; 294:809-811.
15. Tripodi D, Parks LC, Brugmans J. Drug-induced restoration of cutaneous delayed hypersensitivity in anergic patients with cancer. *N Engl J Med* 1973; 289:354-357.
16. Padarathsingh ML, Dean JH, McCay JL, Lewis DD, Northing JW. Restorative effects of levamisole on cell-mediated immune responses following chemotherapy with aniline mustard in mice bearing ADJ-PC5 plasmacytoma. *Cancer Treat Rep* 1978; 62:1627-1635.
17. Chirigos MA, Fuhrman F, Pryor J. Prolongation of chemotherapeutically induced remission of a syngeneic murine leukemia by L-2,3,5,6-tetrahydro-6-phenylimidazo (2,1-b) thiazole hydrochloride. *Cancer Res* 1975; 35:927-931.
18. Gonzales F, Trujillo JM, Alexanian R. Acute leukemia in multiple myeloma. *Ann Intern Med* 1977; 86:440-443.