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Therapy of myeloma [letter]

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CORRESPONDENCE

Therapy of Myeloma

To the Editor:

I would like to comment on Dr. Cohen's article¹ in the *Journal*, employing the combination of BCNU, cyclophosphamide, and prednisone in multiple myeloma and his interpretation of the M-2 results.² There are important differences in the Southeastern Cancer Study Group program that may have affected the results and demonstrate the reported benefits of the M-2. A response³ to an article by Dr. Bergsagel using melphalan and prednisone⁴ has also been submitted for publication.

The important distinctions between these studies are the drugs, doses, and timing of therapy. Melphalan, effective even as a single drug, was not included in Dr. Cohen's paper. Vincristine has been shown to add 9 mo to the remissions attained with multiple alkylating agent programs⁵ and enhances tumor cell kill once the initial labeling index has increased.⁶ Higher doses and more aggressive timing may have compromised the data in the present paper. Four drug deaths were seen, and four patients had therapy discontinued because of toxicity. Moderate to severe nausea and vomiting as well as central nervous system and cardiac problems are described. These side effects and complications were not encountered with the M-2 program with moderate doses and spaced therapy.

The early mortality with the M-2 program is only 5% in the first 15 mo. This success relates to the moderate doses and timing of therapy of the M-2 and the rapid remission (median time to remission, 2 mo) obtained with marked cell kill.³ These results are even more impressive considering the higher proportion of patients

with stage III (74%) in the M-2 compared with 50% in the present study, and the fewer good risk stage I patients in the M-2 (5% versus 28%). Not only is the percentage of remission higher with the M-2, but the survival is doubled. We did not find a significant role for the BUN or type of light chain excreted because of the high remission rate irrespective of these variables, the rapid achievement of a response, and aggressive renal support when necessary. Only one patient has developed acute leukemia after 5.5 yr in remission (with stage III disease). This is compared with the 17.4% actuarial risk in the Bergsagel paper,⁴ suggesting that acute leukemia may be part of the natural history of the disease and that better control of the primary disease process may delay or defer this complication.

In my own series (1976–1979), 20 newly diagnosed consecutively referred patients with stages II and III have been treated with the M-2. All have responded. All are alive except for two patients who expired from unrelated preexisting cardiorespiratory conditions.

I believe the evidence cited confirms the results of the M-2 program in reducing early deaths and producing prompt responses with long-lasting remissions with a low tendency toward acute leukemia. The M-2 program has made a significant contribution to the care and therapy of patients with multiple myeloma.

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2. Case DC Jr, Lee BJ III, Clarkson BD: Improved survival times in multiple myeloma treated with melphalan, prednisone, cyclophosphamide, vincristine, and BCNU: M-2 protocol. *Am J Med* 63:897–903, 1977
3. Case DC Jr: Chemotherapy of multiple myeloma. *N Engl J Med* (submitted for publication)

To the Editor:

We appreciate Dr. Case's comments on our study of BCNU, cyclophosphamide, and prednisone in multiple myeloma¹ and the relationship to the M-2 results.² We agree that there may be many differences between the two studies including those related to the various drug doses and scheduling, as well as those related to potential patient selection differences. The results with the M-2 protocol are very intriguing indeed and should be pursued. However, in order to establish the relationship of the response rate and survival for the M-2 regimen to that of other regimens a concurrent controlled trial will be required. Certainly, uncontrolled trials and small individual studies will not accomplish this.

The danger of making assumptions from historically controlled studies is pointed out by Dr. Case's statement concerning vincristine. In the study cited,³ based on historical controls, the Southwest Oncology Group (SWOG) suggested that vincristine might augment survival when used in combination. However, in a more

4. Bergsagel DE, Bailey AJ, Longley GR, MacDonald RN, White DF, Miller AB: The chemotherapy of plasma-cell myeloma and the incidence of acute leukemia. *N Engl J Med* 301:743–748, 1979

5. Alexanian R, Salmon S, Bonnet J, Gehan E, Weick J: Combination therapy for multiple myeloma. *Cancer* 40:2765–2771, 1977

6. Salmon SE: Expansion of the growth fraction in multiple myeloma with alkylating agents. *Blood* 45:119–129, 1975

recent SWOG study using concurrent controls, the addition of vincristine to an alkylating agent combination does not appear to result in a significant survival advantage.⁴ Moreover, since those myeloma patients who achieve a durable remission are those who continue to have a low labeling index,⁵ it is not clear whether even the theoretic basis for the use of vincristine in this situation is valid.

In any event we feel that only a study that compares alternative regimens concomitantly under controlled circumstances and in comparable patient groups will conclusively establish a response or survival advantage. We certainly look forward to such studies in the future.

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