To the Editor:

Dimopoulos et al. have recently reported the lack of activity of 2-chlorodeoxyadenosine (2-CdA) in multiple myeloma (MM). They treated 10 patients with 0.1 mg/kg/d for 7 days in a continuous infusion. No response was seen in 3 previously untreated, 5 primary refractory, and 2 patients "relapsing despite VAD." Therefore, by standard definition, 7 patients had primary resistant disease. Several pertinent comments should be made: (1) The investigators do not propose a statistical endpoint and we think that an accurate efficacy assessment based on 10 patients is insufficient to define the study as a failure. When 14 patients are analyzed and no response is observed, the predicted true response rate is below 20% with 95% confidence. (2) Although the doses administered to these patients were derived from initial phase I studies, the expected myelosuppression associated with this dose was apparently not seen in these MM patients because the cytopenias were only "mild," and insufficient to be defined as maximum-tolerated dose (MTD). In fact, underdosing may be a key issue in the response failure in these patients who may benefit from 0.15 mg/kg/d, 0.20 mg/kg/d, or even 0.25 mg/kg/d with growth factor support. Patients may tolerate up to 11 mg/m^2 without major extra-hematologic toxicities (R. Warrell, personal communication, November 1992). (3) We are puzzled by the investigators' comparison of fludarabine phosphate (FAMP) and 2-CdA. There are numerous reports suggesting that the mechanism of FAMP action is distinct from that of 2-CdA. FAMP, a purine analogue with activity similar to cytarabine (Ara-C), is incorporated into DNA and displays its major action in cycling populations. In contrast, 2-CdA induces DNA strand breaks, nicotinamide adenine dinucleotide (NAD) depletion, and subsequent inhibition of RNA synthesis leading to cell lysis. Recently, it has been proposed that 2-CdA-mediated toxicity in normal and malignant lymphocytes is via induction of programmed cell death (apoptosis). Its ability to damage noncycling cells suggests that the drug could be useful in malignancies with low proliferative potential. Patients with CLL who have previously failed treatment with FAMP have responded subsequently to 2-CdA treatment and complete remissions have been obtained. The investigators' conclusion that "these agents (2-CdA and FAMP) appear to be more effective in specific malignancies that derive from a relatively narrow range of the B-lymphocyte maturation spectrum" implies a fundamental difference in the biology of MM as opposed to other B-cell neoplasias, such as Waldenstrom's macroglobulinemia (WM), rendering the latter more susceptible to treatment with 2-CdA or FAMP. We would like to point out that there is mounting evidence that the self-renewing population in MM, as in other B-cell malignancies, arises at the level of an earlier B-cell precursor or perhaps even a multipotent progenitor. It is conceivable that the cellular origin of WM is similar. Thus, the argument that MM should not be susceptible to therapy with 2-CdA or FAMP because they "have a narrow spectrum of activity within the B-cell progeny" seems unlikely.

RUBEN NIESVIZKY
DAVID SIEGEL
JOSEPH MICHAELI
Division of Hematologic/Oncology
Department of Medicine
Memorial Sloan-Kettering Cancer Center
New York, NY

REFERENCES

RESPONSE

Dr Niesvizky and his colleagues have expressed concern with our negative experience with 2-chlorodeoxyadenosine (2CdA) in the treatment of 10 patients with multiple myeloma (MM). Not only were no responses observed, but no patient reduced myeloma protein even slightly or showed any meaningful slowing of disease progression. Growth of myeloma continued in all three previously untreated patients during the 2 months of 2-CdA treatment. This contrasts with the marked reduction of Waldenstrom's macroglobulinemia (WM), rendering the latter more susceptible to treatment with 2-CdA or FAMP. We would like to point out that there is mounting evidence that the self-renewing population in MM, as in other B-cell malignancies, arises at the level of an earlier B-cell precursor or perhaps even a multipotent progenitor. It is conceivable that the cellular origin of WM is similar. Thus, the argument that MM should not be susceptible to therapy with 2-CdA or FAMP because they "have a narrow spectrum of activity within the B-cell progeny" seems unlikely.

Table 1. Activity of 2-CdA and FAMP in Low-Grade Lymphoid Malignancies

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be a prerequisite for an adequate treatment trial. Yet, we agree that
we have not ruled out with statistical confidence the possibility of
some antitumor effect in the occasional patient who could have been
offered higher doses.

We have not studied the mechanisms of action of fludarabine
phosphate (FAMP) and 2-CdA but we have had a long interest in
the comparative activity of these agents in low-grade lymphoid ma-
lignancies. Chronic lymphocytic leukemia (CLL) and Waldenstrom’s
macroglobulinemia are sensitive to both FAMP and 2-CdA, whereas
MM is not (Table 1).

Dr Niesvizky has argued that these agents are not cross-resistant
in view of the recent report by Juliusson et al2 on the activity of
2CdA in four patients with CLL resistant to FAMP. We have seen
similar activity with 2-CdA in only 1 of 5 patients with Waldenstrom’s
macroglobulinemia resistant to fludarabine.1 A similarly low fre-
cuency of benefit was seen with 2CdA in a large number of patients
with CLL resistant to FAMP treated at our institution. Thus, despite
in vitro data, cross-resistance to both agents is usually present in
patients with these lymphoid malignancies.

These observations confirm the utility of chemotherapy in defining
not only the sensitivity to treatment but also in dissecting the biologic
heterogeneity of these disorders.

MELETIOS A. DIMOPOULOS
HAGOP KANTARJIAN
ELIHU H. ESTEY
RAYMOND ALEXANIAN
Department of Hematology
The University of Texas
MD Anderson Cancer Center
Houston, TX

REFERENCES
1. Dimopoulos MA, Kantarjian HM, Estey EH, O’Brien S,
DeLasalle K, Keating MJ, Freireich EJ, Alexanian R. Treatment of
Waldenstrom’s macroglobulinemia with 2-chlorodeoxyadenosine.
2-chlorodeoxyadenosine in patients with B-cell chronic lymphocytic
2-Chlorodeoxyadenosine for multiple myeloma [letter; comment]

R Niesvizky, D Siegel and J Michaeli