letter to the editor
Haematologica 1996; 81:286-287

PURINE ANALOGS (FLUDARABINE AND 2-CHLORODEOXYADENOSINE) AS APOPTOSIS-INDUCING DRUGS IN CML THERAPY

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Sir,

Fludarabine (Flu) and 2-chlorodeoxyadenosine (2-CdA) are purine analogs with antineoplastic activity in lymphoproliferative malignancies.[1,2] We recently showed *in vitro* the effective role of Flu[3] and 2-CdA[4] in the activation of apoptosis. We observed a dramatic induction of apoptosis *in vitro* by Flu (Figure 1) and 2-CdA on fresh CML cells,[4] with or without the association of IFN-α.

The mechanism behind this is at present unknown, but *in vivo* studies have also suggested therapeutic roles for Flu[5] and 2-CdA[6] in CML patients. We think that programmed cell death may be suppressed in cells carrying the *bcr-abl* transcript and that Flu and 2-CdA might remove this *suppression effect* in the neoplastic cell cycle.

McGahon *et al.*[7] reported that K562, a chronic myelogenous leukemia (CML) cell line expressing the BCR-ABL fusion protein, is resistant to the induction of apoptosis by a number of agents and conditions.[7] They indicate that BCR-ABL acts as an anti-apoptosis gene in CML and suggest that the effect is dependent on this chimeric protein. CML cells may also resist the effects of cytotoxic agents by overexpression of apoptosis-suppressing genes such as *bcl-2* or *ras*.[8,9] These observations indicate that the myeloid expansion in CML may occur via prolongation of cell survival and that the elevated expression of BCR-ABL tyrosine kinase activity may act to suppress apoptosis. They conclude that an antisense approach to inhibit the expression of the apoptosis-suppressing gene in combination with standard chemotherapy may offer a new therapeutic strategy in conditions in which suppression of apoptosis contributes to the development of the malignancy.

In CML cells such as the K562 cell line, due to

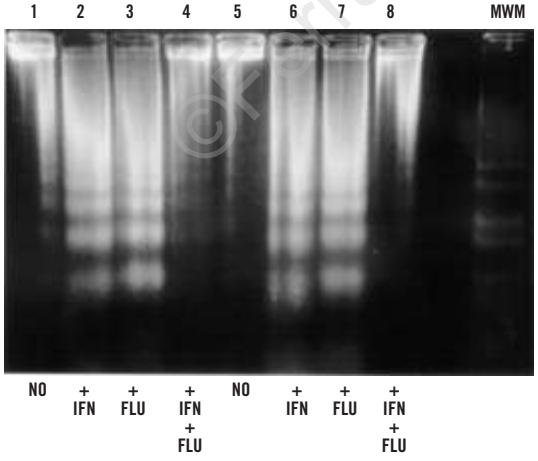

Figure 1. DNA fragmentation pattern of 2 CML patients (lanes 1 to 8). Cells were incubated with: no addition (lanes 1 and 5); 100 U/mL IFN-α (lanes 2 and 6); 50 µg/mL FLU (lanes 3 and 7); IFN-α and FLU combined as described (lanes 4 and 8).[12]
MWM = DNA molecular-weight marker VI, Boehringer Mannheim, Italy.

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Acknowledgments: This work was supported by Associazione Italiana per la Ricerca sul Cancro (A.I.R.C), by Italian C.N.R A.C.R.O. 94.01222.PF39 target projects and by 95.2206 C.N.R. grant. The authors wish to thank Mr. Robin Cooke for checking the English version of the manuscript.

a reciprocal translocation between chromosome 9 and chromosome 22, overexpression of the BCR-ABL protein gives rise to the activation of a RAS-dependent pathway[7,10] and to a large accumulation of mature myeloid cells.[10] The authors argue that the K562 cell line is resistant to cell death through the apoptosis pathway irrespective of the inducing agent used,[11] and they speculate about whether the aberrant expression of the BCR-ABL oncogene seen in K562 cells may contribute to the resistance to apotosis.[12] The putative BCR-ABL anti-apoptotic activity may be opposed by the apoptosis-inducing effects of purine analogs. Taken together, these reports from *in vitro* and *in vivo* studies seem to justify the use of Flu and 2-CdA in pilot clinical trials on chronic phase Ph1$^+$ CML patients.

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