Sir,

Fludarabine (Flu) and 2-chlorodeoxyadenosine (2-CdA) are purine analogs with antineoplastic activity in lymphoproliferative malignancies. We recently showed in vitro the effective role of Flu and 2-CdA in the activation of apoptosis. We observed a dramatic induction of apoptosis in vitro by Flu and 2-CdA on fresh CML cells, 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 and 2-CdA 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. 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. 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. 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...
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 apoptosis.\(^12\) The putative BCR-ABL anti-apoptotic activity may be opposed by the apoptosis-inducing effects of purine analogs. Taken together, these reports from \textit{in vitro} and \textit{in vivo} studies seem to justify the use of Flu and 2-CdA in pilot clinical trials on chronic phase Ph\(^1\) CML patients.

### References