## 15 Toxicities Associated with Purine Analog Therapy

**Bruce D. Cheson**
National Cancer Institute Bethesda, Maryland

### V. Summary

The nucleoside analogs have proven to be highly effective in the therapy of lymphoid malignancies. However, they have a number of associated toxicities, some of what may be severe. Of particular concern is immunosuppression wich is uniform with standard treatment programs. Each of the nucleoside analogs is associated with a profound lymphocytopenia, with a reversal of the CD4/CD8, and opportunistic infections. Whether secondary malignancies will be a long-range complication will require observation and recording of long-term follow-up resulsts.
The frequency with wich many of the nonhematologic toxicities occur is difficult to estimate. Most studies contain small numbers of patients, in whom few, if any nonhematologic toxicities are reported. Whether that reflects the actual rarity of these events or the care with which those series was evaluated is not clear. As the clinical experience with these agents become more extensive, with longer follow-up, recognized toxicities will become better charatrized and new side effects ma be encountered. Anecdotal reports may serve to increase the sensitivity for identification of new and unusual complications.
There are a number of unresolved issues in the use of the nucleoside analogs. The optimal schedule of administration remains unknown. A 6-month course of fludarabine has been recommnded for CLL, and a similar duration of DCF for HCL. Although a single course of CDA is generally used for HCL, repeated courses have been delivered for the other lymphoid malignancies.
Nevertheless, these regiments are empiric. An accumlating body of evidence suggests that fludarabine and CdA work by a different mechnism of action, e.g., activation of apoptosis. Therefore, we may be administering more drug than is required for biological effect (199, 200). Further study of this issue is warranted to maintain efficacy while minimizing the tocicities associated with treatment with these highly effecive nucleosid analogs. As nucleosid analogs are being combined with cytotoxic and biological agents in an attempt to increase their efficacy, care must be exercised to avoid drugs with overlapping toxicities.
Based on the published literature, the non-hematologic toxicities from the nucleoside analogs are relatively similar (Table 3), with the possible exception of the ocular toxicity, rash and increased severity of nausea and vomiting with DCF, and the relatively more prolonged period of immunosuppression with DCF and CdA. In general, however, they are relatively well tolerated. The decision as to which is the preferred nucleoside analog for a specific indication must be determined by their response rate, durability of responses, cost, toxicity profile and ease with wich they can be combined into effective combination regiments.

## 2 Induction of Apoptosis by Nucleoside Analogs

**Peng Huang**
The University of Texas, M.D. Anderson Cancer Center, Houston, Texas
**Susan Wright**
Mater Hospital, South Brisbane, Australia

### V Summary

Apoptosis is a key pathway by which nucleoside analogs exert their cytotoxic action against cancer cells. Although this class of drugs acts at multiple cellular targets, the incorporation of the analogs into cellular DNA is a crtical event in triggering apoptotic response. In proliferating cell population, S-phase cells are most sensitive to apoptosis induction. Two distinct size classes of DNA fragmentation, the internucleosomal and high molecular weight DNA fragments, are associated with nuceloside analog-induced apoptosis. The two types of DNA fragmentation are distinguishable by their requirements for Ca2+ and responses to phorbol ester treatment. High molecular weight DNA fragmentation is an early event of DNA degradation that is critical for drug-induced apoptosis, wheras activation a Ca2+-dependent endonuclease to cleave DNA at internuclesomal sites is not an absolute requirement for the execution of the apoptotic cell death program. Furthermore, high molecular weight DNA fragmentation occurs in vivo and may be correlated with the therapeutic activities of nucleoside analogs.

The factor responsable for high molecular weight DNA fragmentation is a protein that requires MG2+, ATP, and neutral pH for optimal activity. This activity is transferable by cell fusion and active in isolated nuclei. Thus, the enzyme responsible for clevage of DNA int HMW fragments may be considered as an execution molecule in the apoptotic process. Figure 7 illustrates a proposed model of nucleoside analog-induced apoptosis. During DNA replication, cells maintain a normal level of DNA repair activity and keep the apoptotic program inactive through the function of the proposed sensor molecule (e.g., DNA-PK/Ku). The incorporation of analogs into DNA terminates further strand elongation, resulting in the generation of an abnormal DNA end. A sensor molecule binds to the damaged DNA region and singals for repair. If repair fails, the sensor molecule triggers the apoptotic program by phosphorylating other proteins involved in the signaling and execution of the cell death pathway. This apoptotic mechanism can be regulated by a variety of regulatory molecules such as bcl-2, bcr-abl, p53, and c-myc. A comprehensive understanding of the mechanisms in drug induced apoptosis and ist regulation will provide a base for developing more effective therapeutic strategies for cancer treatment.

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