EVALUATION OF AN INHIBITOR OF DNA METHYLATION, 5-AZA-2'-DEOXYCYTIDINE, FOR THE TREATMENT OF LUNG CANCER AND THE FUTURE ROLE OF GENE THERAPY

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1. INTRODUCTION

The antineoplastic activity and pharmacology of 5-aza-2'-deoxycytidine (5-AZA-CdR) have been under investigation in our laboratory for some time (Momparler, 1985). The chemical structures of 5-AZA-CdR and its related natural nucleoside, deoxycytidine, are shown in Fig. 1. The only structural difference between these two compounds is the presence of a nitrogen at position 5 of the cytosine ring in 5-AZA-CdR as compared to a carbon at this position for deoxycytidine. In this article we will review the pharmacology of 5-AZA-CdR, its preliminary antitumor activity in patients with advanced non-small cell lung cancer (NSCLC), and the possible use of gene therapy to improve its anticancer effect.

1.1. Pharmacodynamics of 5-AZA-CdR

5-AZA-CdR is a prodrug that must first be phosphorylated to be converted to its active form. The rate limiting enzyme for this metabolic activation is deoxycytidine kinase (Fig. 2). The affinity of 5-AZA-CdR for the catalytic site of this enzyme is similar to that of the natural substrate, deoxycytidine (Momparler, 1985). Deoxycytidine kinase is
primarily synthesized during the S phase of the cell cycle. Cells deficient in this enzyme are completely resistant to 5-AZA-CdR.

Another key enzyme involved in the action of 5-AZA-CdR is DNA polymerase. 5-AZA-CdR, after conversion to its triphosphate form, 5-AZA-dCTP, is incorporated into replicating DNA at a rate similar to that of the natural substrate, dCTP (Bouchard and Momparler, 1983). The major pharmacological characteristics of 5-AZA-CdR are summarized in Table 1. The antineoplastic action of 5-AZA-CdR is S phase specific (Momparler, Samson, Momparler, and Rivard, 1984). This analogue produces a marked loss of clonogenicity for many types of leukemic and tumor cell lines, as determined by colony assay. 5-AZA-CdR has been demonstrated to induce terminal differentiation of both embryonic and neoplastic cells (Momparler, Bouchard, and Samson, 1985a; Jones and Taylor, 1980). The plasma half-life of 5-AZA-CdR in man is short, in the range of 15 to 20 min (Momparler, Rivard, and Gyger, 1985b), and this is due primarily to deamination of this analogue by the high levels of cytidine deaminase in the liver (Ho, 1973). In animal