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# Forodesine

Nucleoside analogs have played a major role in treatment of hematological malignancies including lymphomas. While they are not targeted agents, deoxyguanosine and its analog appear to be selective. This is based on the discovery that the rare deficiency of the enzyme purine nucleoside phosphorylase (PNP) in children causes profound T-cell lymphopenia. This observation provided a rationale for development of PNP inhibitors. Consistent with the catabolic role of this enzyme on the substrate deoxyguanosine (dGuo), there was an increase in the level of plasma dGuo in these patietns. T-cell specificity was due to the inherently greater phosphorylation of dGuo and slower catabolism of the tri-phosphorylated dGuo (dGTP) in this subtype of cells. This, in turn, perturbs the optimal concentration of dNTP pool leading to dGTP-directed inhibition of DNA synthesis and cell death. Mammalian PNP searches for oxo at the 6-position of the base and hence only takes (2'-deoxy)guanosine and inosine as substrates. Based on the substrate conversion during phosphorolysis process, Vern Schramm's group synthesized forodesine (immucillin hypoxanthine or BCX-1777) a potent inhibitor of the PNP enzyme. Preclinical investigations established utility of this agent in inhibiting PNP, maintaining dGuo in the medium, accumulating dGTP in T-cell lines and inducing apoptosis. First clinical investigation with this agent served as a proof-of-concept study to demonstrate almost complete inhibition of the enzyme in red blood cells. In parallel, there was an increase in plasma dGuo level and dGTP accumulation in circulating T-cells. Consistent with the hypothesis, there was a relationship between intracellular concentration of dGTP and pharmacodynamic response measured as clearance of T-leukemic cells. This was the first demonstration in human that forodesine is an effective inhibitor of PNP and PNP suppression leads to plasma dGuo and cellular dGTP accumulaiton. Additional clinical investigations suggested utility of this agent in T-cell lymphoma and B-cell leukemias such as B-ALL and B-CLL. However, the most profound effect was always in the T-cell lineage diseases.

## References

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