An Overview of the Clinical Pharmacology of N-Phosphonacetyl-L-Aspartate (PALA), a New Antimetabolite

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N-Phosphonacetyl-L-aspartic acid (PALA) is a new synthetic antimetabolite which inhibits de novo pyrimidine biosynthesis. Its significant activity against Lewis lung carcinoma, B16 melanoma, and glioma 26 suggested that it might be useful in the treatment of human solid tumors. Phase I trials revealed that dose-limiting toxicity included skin reactions, diarrhea, and stomatitis. Pharmacologic studies demonstrated rapid renal excretion of more than 70% of the unmetabolized drug in 24 h. Peak plasma levels correlated with dose of PALA administered. Partial responses to PALA were seen in one patient with melanoma, one with chondrosarcoma, and one with colon carcinoma. The potential for PALA’s use in combination chemotherapy, particularly with 5-fluorouracil, is discussed.

Introduction

N-Phosphonacetyl-L-aspartic acid (PALA) was synthesized by Collins and Stark [2] as an analogue of the transition state intermediate of the reaction catalyzed by aspartate transcarbamylase (ATC). This reaction, whereby carbamyl phosphate and aspartate combine to form carbamylaspartate, is the second step in de novo pyrimidine biosynthesis (Fig. 1). PALA competitively inhibits the binding of carbamyl phosphate to ATC with a $K_i$ of approximately $10^{-8}$ M. In Escherichia coli, ATC is a key enzyme in de novo pyrimidine biosynthesis. Thus, inhibition of this enzyme by PALA significantly diminished pyrimidine biosynthesis. However, carbamyl synthetase, and not ATC, is the rate-limiting enzyme in the de novo pathway of pyrimidine biosynthesis in mammalian cells [11]. Furthermore, a “salvage pathway” for pyrimidine nucleotide biosynthesis potentially exists in mammalian cells which could supply the necessary precursors either preferentially or in the case of inhibition of the de novo pathway. Despite these two potential biochemical drawbacks, PALA has demonstrated interesting antineoplastic activity in murine systems. On this basis and its predictable, tolerable, and reversible toxicity in animals, PALA has undergone phase I trial in the United States in the past year. This paper presents some of the pertinent preclinical data and a summary of the phase I results and discusses possible future roles for PALA as a new antimetabolite in the study and therapy of cancer.

Preclinical Studies of PALA

PALA was screened in a variety of murine tumors and demonstrated an unusual spectrum of activity. It had significant activity against Lewis lung carcinoma, B16
De novo

\[
\text{CO}_2 + \text{Mg} - \text{ATP} + \text{glutamine} \rightarrow \text{Carbamyl phosphate + aspartate} \rightarrow \text{Carbamylaspartate}
\]

Salvage

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\text{Uracil + ribose-1-PO}_4 \rightarrow \text{Uridine + Mg - ATP} \rightarrow \text{UMP} \rightarrow \text{UTP}
\]

**Fig. 1.** Pathways for pyrimidine biosynthesis. Mg, Magnesium; ATP, adenosine triphosphate; UMP, uridine monophosphate; UTP, uridine triphosphate