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# A PHASE I AND PHARMACOKINETIC (PK) STUDY OF THE MULTITARGETED ANTIFOL (MTA) LY231514 WITH FOLIC ACID (Meeting abstract).

Sub-category:
Other

Category:
Developmental Therapeutics - Clinical Pharmacology and Immunotherapy

Meeting:
1998 ASCO Annual Meeting

Abstract No:
866

Author(s):
L Hammond, M Villalona-Calero, SG Eckhardt, R Drengler, C Aylesworth, T Johnson, M Hidalgo, G Rodriguez, S Diab, P Monroe, D Thornton, Hoff D Vo, E Rowinsky

Abstract:

MTA (LY 231514) is a new antifol that inhibits multiple folate-dependent enzymes, including thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase. Initial phase I trials demonstrated major antitumor responses when MTA was given as a 10 min I.V. infusion, however, myelosuppression precluded dose escalation above 500-600 mg/m2. Since preclinical studies indicated that folic acid supplementation increases the eherapeutic index of MTA, the feasibility of administering folic acid 5 mg daily for 5 days starting 2 days before MTA in minimally- and heavily-pretreated pts was evaluated to determine if folic acid supplementation ameliorates the toxif effects of MTA, permitting significant dose-escalation above the recommended phase II dose of MTA alone. Thus far, 21 pts with solid cancers have received 55 courses at the following dose levels: 600, 700, and 800 mg/m2. Drug-related toxicities have included neutropenia, anemia, and thrombocytopenia, which have been more severe in heavily-pretreated pts. Other toxicities (grade 1-2) include rash, somnolence, fatigue, leg edema, and diminished renal function manifested by a decrease in creatinine clearance. One pt taking a non-steroidal anti-inflammatory agent experienced severe toxicities at the 800 mg/m2 dose, which resolved after administration of leucovorin and thymidine. One partial response in a pt with metastatic colon cancer has been observed. PK and vitamin (folic acid) metabolite profiles were done during cycles 1 and 3 at 600 to 800 mg/m2. To date, serum folic acid levels do not appear to be related to toxicity, but homocysteine was significantly elevated in the pt with severe toxicities at the 800 mg/m2 dose. Thus far, heavily- and minimally-pretreated patients have tolerated MTA at 600 and 800 mg/m2 and accrual continues at 700 and 900

mg/m2, respectively. These results indicate that folic acid supplementation appears to permit MTA dose escalation.

- Associated Presentation(s):

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  Meeting: 1998 ASCO Annual Meeting Abstract No: 715 First Author: Stewart C
  Category: Developmental Therapeutics - Clinical Pharmacology and Immunotherapy - Other
  2. POPULATION PHARMACOKINETIC (PK) MODEL FOR TOPOTECAN (TPT) (Meeting abstract).

  Meeting: 1998 ASCO Annual Meeting Abstract No: 716 First Author: PB Laub
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  1. ILX651 administered daily for five days every 3 weeks (qdx5dq3w) in patients (pts) with inoperable locally advanced or metastatic melanoma:phase II experience

  Meeting: 2005 ASCO Annual Meeting Abstract No: 7556 First Author: D. F. McDermott
  Category: Melanoma/Skin Cancers - Melanoma
  2. A phase I pharmacokinetic (PK) trial of XAA296A (Discodermolide) administered every 3 wks to adult patients with advanced solid malignancies.

  Meeting: 2004 ASCO Annual Meeting Abstract No: 2025 First Author: A. Mita
  Category: Developmental Therapeutics - Clinical Pharmacology and Immunotherapy - Pharmacology/Pharmacokinetics
  3. A pharmacologic and metabolic study of docetaxel (D) administered on a continuous weekly schedule in patients with advanced solid tumors.

  Meeting: 2003 ASCO Annual Meeting Abstract No: 651 First Author: J. D. Rizzo
  Category: Developmental Therapeutics - Clinical Pharmacology and Immunotherapy - Pharmacology/Pharmacokinetics
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- Presentations by L Hammond:

  1. Phase (Ph) I evaluation of the dolastatin analogue synthadotin (SYN-D; ILX651): Pooled data analysis of three alternate schedules in patients (pts) with advanced solid tumors.

  Meeting: 2004 ASCO Annual Meeting
  Presenter: Lisa A. Hammond, MD
  Session: Developmental Therapeutics: Molecular Therapeutics (General Poster Session)
  2. Phase 1 study of pemetrexed (LY231514) with vitamin supplementation in patients with locally advanced or metastatic cancer

  Meeting: 2003 ASCO Annual Meeting
  Presenter: Lisa A Hammond, MD
  Session: Developmental Therapeutics - Cytotoxic Chemotherapy (General Poster Session)
  3. Phase I and pharmacokinetic (PK) trial of sequences of the rebeccamycin analog, NSC 655649, and cisplatin (CDDP)

  Meeting: 2002 ASCO Annual Meeting
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