Eur J Cancer Clin Oncol, Vol. 18, No. 1, pp. 113–114, 1982.
Printed in Great Britain.

0277-5379/82/010113-02$03.00/0

Letter to the Editor

Protective Effect of *N*-acetylcysteine on the Urotoxicity Produced by Oxazaphosphorine Without Interference with Anticancer Activity

L. R. MORGAN*, P. J. DONLEY*, E. F. HARRISON† and H. L. HUNTER†

**Department of Pharmacology and Medicine, Louisiana State University Medical Center, New Orleans, Louisiana 70112, U.S.A. and †Pharmaceutical Medical Research, Mead Johnson Pharmaceutical Division, Evansville, Indiana 47721, U.S.A.*

A RECENT article by Brock *et al.* [1] cited references that supported the thesis that *N*-acetyl-L-cysteine (NAC) was not clinically effective as an uroprotective agent because NAC interfered with the antitumor activity of the oxazaphosphorines. They reference Connors [2], who reported on the interaction of cysteine and Merophan (*o*-di-2-chloroethylamine-DL-phenylalanine), and Ishidate *et al.* [3], who studied the interference of cysteine on Nitromin toxicity. Neither of these agents are oxazaphosphorines and we disagree that NAC interferes with the antitumor effect when administered simultaneously with oxazaphosphorines.

Kline *et al.* [4] reported protection against toxicity to the host and enhanced antitumor activity when NAC was administered simultaneously with, 1 hr prior to, or 10 min after ifosfamide (an oxazaphosphorine) to mice with L1210 leukemia. Cox [5] found no significant difference between the antitumor activity of cyclophosphamide alone or in combination with NAC using the Walker 256 carcinosarcoma test model in rats. Tolley [6] agreed with this observation using a similar animal test model.

In our clinic, a randomized pilot study was conducted designed to evaluate the uroprotective properties of NAC when administered during ifosfamide treatment of lung cancer [7, 8]. We observed objective tumor responses (1 complete, 1 partial) in the ifosfamide + NAC group. A similar objective response rate was observed in the ifosfamide alone-treated group. Ifosfamide was administered intravenously at 1.2 g/m^2/day for 5 days, and NAC was given orally 1 g every 6 hr for 5 days beginning 1 hr before ifosfamide therapy. Hematuria was adequately controlled in the NAC treated patients.

We conclude from these limited clinical observations that NAC does not significantly interfere with the antitumor activity of ifosfamide, which is an alkylating agent of the oxazaphosphorine class. Further clinical studies are ongoing.

Accepted 16 September 1981.

REFERENCES

1. BROCK N, POHL J, STEKAR J. Studies on the urotoxicity of oxazaphosphrine cytostatics and its prevention—I. Experimental studies on the urotoxicity of alkylating compounds. *Eur J Cancer* 1981, **17**, 595–607.
2. CONNORS TA. Protection against the toxicity of alkylating agents by thiols: the mechanism of protection and its relevance to cancer chemotherapy. *Eur J Cancer* 1966, **2**, 293–305.
3. ISHIDATE M, SAKURAI Y, YOSHIDA T, SATOH H, MATSIU E, IMAMURA H. Studies on the toxicity of "Nitromin" Interference of cysteine upon "Nitromin" toxicity. *Gann* 1953, **44**, 386–389.

4. KLINE I, GANG M, WOODMAN RJ, CYSYK RL, VENDITTI JM. Protection with *N*-acetyl-L-cysteine (NSC-111180) against isophosphamide NCS-109724) toxicity and enhancement of therapeutic effect in early murine L1210 leukemia. *Cancer Chemother Rep* 1973, **57**, 299–304.
5. COX PJ. Cyclophosphamide cystitis—Identification of acrolein as the causative agent. *Biochem Pharmacol* 1979, **28**, 2045–2049.
6. TOLLEY DA. The effect of *N*-acetylcysteine on cyclophosphamide cystitis. *Br J Urol* 1977, **49**, 659–661.
7. MORGAN LR, DONLEY PJ, HARRISON EF. The control of ifosfamide-induced hematuria with *N*-acetylcysteine. *Clin Pharmacol Ther* 1981, **29**, 266–267.
8. MORGAN LR, DONLEY PJ, HARRISON EF. The control of ifosfamide-induced hematuria with *N*-acetylcysteine. *Proc Amer Assoc Cancer Res* 1981, Abstract 754, 190.