Eur J Cancer Clin Oncol, Vol. 24, No. 4, pp. 799–800, 1988.
Printed in Great Britain

0277-5379/88$3.00+0.00

Letter to the Editor

The Use of Diamox in the Sequential Methotrexate–5-Fluorouracil Therapy of Advanced Gastrointestinal Cancer

TATSUO ABE,*†‡ HIROMI YASHIGE,† JOHJI INAZAWA,* SHOUHEI YOKOTA,† SHOICHIRO TSUDA,† MASAFUMI TANIWAKI,† SOROU TAKEDA,† SHINICHI MISAWA† and TATSURO TAKINO†

**Department of Hygiene and †Department of Medicine, Kyoto Prefectural University of Medicine, Kamigyoku, Kyoto* 602, *Japan*

CHEMOTHERAPY with sequential methotrexate (MTX) and 5-fluorouracil (5-FU) treatment has been used to treat advanced cancer. The mechanism of interaction of these drugs is of particular interest: MTX antagonizes dihydrofolate reductase (DHFR) causing the depletion of intracellular reduced folate and, thus, *de novo* pyrimidine synthesis is blocked. *De novo* purine synthesis is also inhibited, resulting in an expanded intracellular PRPP pool; the increased PRPP is utilized to promote the conversion of 5-FU to 5-FdUMP [1]. The synergistic effect of MTX and 5-FU has been shown in various cancer and leukemia cell lines [1, 2], when the two drugs are used in sequence. Using MTX first seems to produce more favourable effects. However, the optimum interval between the administration of the drugs has not been determined [2]; this lack reflects the complexities of the *in vivo* pharmacokinetics. Toxicity associated with this therapy regimen has been reported even at a moderate dose (100–200 mg/m^2) of MTX [3–5]. This may be attributed to a direct toxic effect on renal tubules, since changes in BUN occur that correlate with clinical and hematologic toxicity [6]. The toxicity is a limiting factor in choosing the MTX + 5-FU regimen for cancer chemotherapy.

We have treated 13 patients with advanced gastrointestinal cancer with a revised MTX + 5-FU regimen. Toxicity due to MTX was prevented remarkably by the use of acetazolamide (Diamox®) and other modifications, such as using sodium bicarbonate and hydration. We have used the following protocol: a tablet containing 250 mg Diamox was given orally to patients 30 min before the start of therapy. Then, a drip infusion of 500 ml of maintenance solutions containing 60 ml of 7% sodium bicarbonate was started. Simultaneously, MTX (100 mg/m^2) was given by intravenous infusion. One hour later, a 30 min-drip infusion of 5-FU (600 mg/m^2) was started. Three hours later another tablet of Diamox was given. This regimen was repeated at 7-day intervals.

When we began to use MTX in cancer chemotherapy, a few patients suffered from toxicity even after a single dose of 30 mg/m^2 MTX. Severe stomatitis and mucositis developed in two older patients who had been given trichlormethiazide to treat hypertension. Since the use of Diamox and 7% sodium bicarbonate solution was recommended in cases of high-dose MTX treatment, we added these drugs to the protocol. In each patient more than six courses of MTX and 5-FU regimen were given. Except for nausea and lassitude observed in some patients immediately after treatment, most patients who entered this trial had no toxicity during treatment. Also no leukopenia and

Accepted 16 November 1987.
‡Author to whom correspondence and reprint requests should be addressed: Dr. Tatsuo Abe, Department of Hygiene, Kyoto Prefectural University of Medicine, Kamigyoku, Kyoto 602, Japan.

thrombocytopenia were observed in any of 13 patients. Fujimoto and co-workers [7–9] reported that adequate hydration of urine is essential for high-dose MTX treatment at doses over 2.0 g/m^2 and intermediate dose (150 mg/m^2) infusions of MTX without LV rescue is promising. In fact, rescue therapy with a citrovorum factor was no longer needed. The clinical effects on the advanced gastrointestinal cancer were marked; of the 13 patients treated, a complete response was noted in one, a partial response in six and a minor response in three. A total of five patients had a long symptom-free interval and were able to work during treatment. They achieved a fairly good quality of life.

Details of this clinical trial will appear elsewhere.

REFERENCES

1. Cadman EC, Heimer R, Davis L. Enhanced 5-fluorouracil nucleotide formation after methotrexate administration: explanation for drug synergism. *Science* 1979, **250**, 1135–1137.
2. Bertino JA. Clinical application of the scheduled combination of methotrexate and 5-fluorouracil. In: Bertino JR, ed. *The Chemotherapy of Breast, Gastrointestinal and Head and Neck Cancer. Current Status and Potential Role of Methotrexate and 5-Fluorouracil.* Chicago, Pharma-Libri, 1983, 109–120.
3. Weinerman B, Schacter B, Schipper H, Bowman D, Levit M. Sequential methotrexate and 5-FU in the treatment of colorectal cancer. *Cancer Treat Rep* 1982, **66**, 1553–1554.
4. Bruckner HW, Cohen J. MTX/5-FU trials in gastrointestinal and other cancers. *Semin Oncol* 1983, **10**, 32–39.
5. Kemeny NE, Ahmed T, Michaelson RA, Harper HD, Vip LC. Activity of sequential low-dose methotrexate and fluorouracil in advanced colorectal carcinoma: attempt at correlation with tissue and blood levels of phosphoribosylpyrophosphate. *J Clin Oncol* 1984, **2**, 311–315.
6. Condit PT, Chanes RE, Joel W. Renal toxicity of methotrexate. *Cancer* 1969, **23**, 126–131.
7. Sasaki K, Tanaka J, Fujimoto T. Theoretically required urinary flow during high-dose methotrexate infusion. *Cancer Chemother Pharmacol* 1984, **13**, 9–13.
8. Sasaki K, Tanaka J, Murakami T, Matuoka H, Fujimoto T, Taguchi H. Reduced citrovorum factor rescue for high-dose methotrexate therapy in childhood malignancies. *Cancer Drug Deliv* 1985, **2**, 77–85.
9. Fujimoto T. Methotrexate therapy in acute leukemia in children. In: Kimura K, Wang YM, eds. *Methotrexate in Cancer Therapy.* New York, Raven Press, 1986, 146–160.