Eur J Cancer Clin Oncol, Vol. 17, No. 9, pp. 1061–1062, 1981.
Printed in Great Britain.

0277-5379/81/091061-02$02.00/0

Letter to the Editor

Thioproline (Norgamem): a Useless Drug in the Treatment of Squamous Cell Carcinoma

PIERRE ALBERTO
Division d'Onco-Hématologie, Hôpital Cantonal, Universitaire, 1211 Genève 4, Switzerland

For the E.O.R.T.C. Early Clinical Trial Group

IN A RECENT communication [1] Brugarolas and Gosalvez reported 13 objective responses in 15 cancer patients treated with thioproline (thiazolidine - 4 - carboxylic acid, "Norgamem"), given i.v. or im. at a dosage of 20 or 40 mg/kg daily for 5 days or longer. Of 10 patients with advanced squamous cell carcinoma of the head and neck, all responded. This report raised considerable interest since this high response rate was apparently obtained with no drug-related toxic effects. Based on limited experimental data [2], it was speculated that thioproline could restore cell differentiation and contact inhibition in malignant cells. This proposed mechanism of action made it particularly attractive among all anti-cancer agents.

We wish to summarize briefly the results of a Phase II trial with thioproline in patients with squamous cell carcinoma. This trial was conducted by the Early Clinical Trial Group of the European Organization for Research on Treatment of Cancer.

Patients with histologically proven squamous cell carcinoma of the oral cavity, pharynx, larynx and lung were eligible, provided they were not amenable to surgical or radiotherapeutical treatment and had not received previous chemotherapy. Further requirements included measurable tumor lesions, documented tumor progression, performance status score of 50% or more (Karnofsky's scale) and normal bone marrow, liver and renal functions. Tumors were histologically classified as well-differentiated carcinoma (indicating the presence of keratin or intercellular bridges over most of the tumor) or as moderately/poorly-differentiated carcinoma. The drug was given i.m. at a dose of 10 mg/kg repeated every 6 hours for at least 3 weeks. Tumor responses were categorized as response (decrease of initial measurements by 50% or more), stable disease, progression and early death. Thioproline was supplied by Dr. Gosalvez as a lyophilized powder in vials containing 250 mg for injection of a sodium salt of the agent to be dissolved in 2.5 ml of sterile water.

Thirty-seven patients received thioproline. Thirty-three were evaluable for tumor response, 22 with a tumor of the head or neck and 11 with a tumor of the lung. Twelve had well-differentiated carcinoma and 12 had moderately or poorly-differentiated carcinoma. The grade of cell differentiation could not be obtained for 9 tumors. Sixteen patients had locoregional disease and 17 had distant metastases. No tumor responses were observed. One patient died 2 weeks after initiation of treatment. For the other patients, the duration of treatment ranged from 2 to 13 weeks (median: 5.8 weeks for head and neck tumors, 4.3 weeks for lung tumors). At the end of treatment the tumor was progressive in 22 patients and not progressive in 10 patients. Toxic effects consisted of gluteal abcesses (3 patients) and mental disturbances (7 patients) manifested by confusion, aggressiveness or mental depression. Neurological toxicity was reversible in all but one patients upon discontinuation of therapy.

Thus, the previously reported anti-tumor activity of thioproline in squamous cell carcinoma could not be reproduced with an identical dose schedule in the present multicentric trial. Although local or neurological complications were relatively infrequent, the treatment was poorly tolerated by most patients, due to the large number of intramuscular injections.

REFERENCES

1. BRUGAROLAS A, GOSALVEZ M. Treatment of cancer by an inducer of reverse transformation. *Lancet* 1980; **i:** 68–70.
2. GOSALVEZ M, VIVERO C, ALVAREZ I. Restoration of "contact inhibition" in tumor cells in tissue culture by treatment with thiazolidine-4-carboxylic acid. *Biochem Soc Trans* 1979; **7:** 191–192.