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Nitrosourea Derivatives-Induced Pulmonary Toxicity in Patients Treated for Malignant Brain Tumors. Early Subclinical Detection and its Prevention

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Abstract—*Nitrosourea derivatives, such as BCNU and CCNU, are considered useful chemotherapeutic agents in malignant brain tumors combined therapy. Pulmonary toxicity is one of the major side effects demonstrated both in experimental animal models and in human autoptic findings. Pulmonary fibrosis is the end point of progressive functional disorder of respiratory mechanism and alveolo-capillary gas exchanges. Authors present the results of a randomized, double-blind trial of 40 patients previously treated with surgery and radiotherapy and who subsequently underwent BCNU therapy for primary intracranial glioma. Patients underwent functional respiratory examinations at each chemotherapy course interval. Twenty patients received ambroxol (120 mg/day) for 40 days after chemotherapy course. Control patients received placebo with the same schedule and showed a significant reduction of pulmonary functional parameters (DLCO, MMEF, MEF 25%), whereas in the treated group there is no significant variation of these functional parameters. The mechanism of ambroxol is commonly related to the surfactant synthesis enhancement and to the action on bronchiolar pathways.*

INTRODUCTION

IT IS WELL known that nitrosourea derivatives, such as BCNU and CCNU, are considered chemotherapeutic agents with proven activity in the adjuvant treatment of human malignant brain tumors [1]. Side-effects primarily involve the hematopoietic system (leuko-piastrinopenia) and gastrointestinal tract (nausea, vomiting), while liver toxicity and renal impairment are not commonly reported as important complications [2]. Recently, pulmonary fibrosis has been reported in long-term survival patients as another feature of clinical toxicity of nitrosourea derivatives. Schmidt *et al.* have demonstrated in a canine experimental model the genesis of pulmonary toxicity induced by nitrosourea compounds (quoted by Durant *et al.* [3]). There is evidence of an initial exudative phase with characteristic edema and damage of Type I pneumocytes. Then, it appears, hyperplasia of Type II pneumocytes, endothelial cells and fibroblasts leading to interstitial fibrosis [4]. The pathogenetical mechanism is still unclear: there is evidence for a direct toxic effect of cytostatic drug on nucleic acids [5], or for a possible involvement of oxidating radicals released by inflammatory and immuno-effector cells [6]. Recently, prostaglandins, too, have been investigated as a possible mediator system of functional damage of Type II pneumocytes [5, 7]. Anyway, Rosenow defined two clinical presentations in man [8]: the first an acute, dose-dependent, eosinophilic-pneumonia-like with characteristic pulmonary edema, and the second, a chronic lung disease with progressive structural changes in the alveolo-capillary junctions evolving to pulmonary fibrosis. The fibrosis seems to appear for an estimated cumulative dose over 1500 mg/m^2 of BCNU [9]. The first case of pulmonary toxicity induced by BCNU was desribed by Holoye *et al.* [10]. Selker *et al.* have reported 14 cases of autoptic controlled pulmonary fibrosis in patients treated with nitrosourea derivatives [9]. Other case

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reports are available in literature [3, 11]. Thus pulmonary fibrosis is a rare complication of a long-term adjuvant chemotherapy with nitrosourea compounds, but abnormalities in some functional parameters, including alveolo-capillary gas exchanges, could be detected in a sub-clinical stage of pulmonary disease.

MATERIALS AND METHODS

This randomized, double-blind, controlled study was designed to verify whether ambroxol (Mucosolvan, De Angeli Inc., Milan, Italy), a drug enhancing alveolar surfactant synthesis [12] and modulating inflammatory cells afflux to alveolo-capillary structures [13], can play a role in the prevention of BCNU-induced pulmonary toxicity in patients treated for malignant brain tumors. From January 1, 1983 to December 31, 1984, 40 patients, with the diagnosis of malignant glioma (27 glioblastomas and 13 anaplastic astrocytomas), were admitted to the study (Table 1). Patients underwent surgery at the Neurosurgical Section of the Department of Surgery, University of Pavia, Italy. Eligibility criteria included: age over 20 years, pre-operative Karnofsky performance status ≥ 60, anticipated survival time of at least 6 months, cigarette-smoking history negative. Patients with previous abnormal pulmonary function were excluded from the protocol. After surgery, all patients underwent radiotherapy (45–50 Gy whole brain plus 10–15 Gy on the tumoral bed) with megavoltage equipment. Chemotherapy courses with BCNU (220 mg/m^2 i.v.) and clinical and radiological controls were repeated every 8 weeks. Under basal conditions (before the beginning of chemotherapy) and at every chemotherapy course, the following tests were carried out to evaluate respiratory function: vital capacity (VC), residual volume (RV), total lung capacity (TLC), forced expiratory volume in 1 sec (FEV 1%), medium–maximal expiratory flow (MMEF), maximal expiratory flow at 25% of vital capacity (MEF 25%), diffusing capacity for carbon monoxide (DLCO), diffusing capacity/ventilation (DLCO/V) with the Ogilvie's method [14] and blood gases analysis. Drug-induced toxicity was assessed every 8 weeks with analysis of hematological parameters, renal and liver functional examinations. Twenty patients were randomized for ambroxol treatment (40 mg orally, 3 times a day, for 40 days, starting at day 10 after chemotherapy course). Twenty control patients received placebo following the same schedule. Patients were considered as evaluable after, at least, 3 respiratory functional tests (T_3). The analysis of each functional parameter was referred to the pre-operative basal control (T_0).

Table 1. Clinical characteristics of 40 patients entered into the study

	Ambroxol	Placebo
Randomized patients	20	20
Evaluable patients	18	16
Average age	54	57
Range (years)	24–65	27–67
Histopathological diagnosis		
Glioblastoma	15	12
Anaplastic astrocytoma	5	8
Average chemotherapy courses	6	6
Range	3–10	3–9
Average dose BCNU (mg/m^2)	1290	1300
Average survival (weeks)	54	56

RESULTS

Clinical characteristics of patients entered into the study are reported in Table 1. Pre-operative Karnofsky performance status was 60 in 5 cases of both groups; duration of follow-up from date of surgery ranged between 7 and 22 months. Actuarial survival rate at 12 months after surgery was 68.5% with a median survival time of 16.5 months. Toxic effects from chemotherapy were mostly nausea and vomiting, leukopenia and thrombocytopenia, without differences from our previous experiences [1, 2, 15]. In no cases did chest radiographs demonstrate signs of pulmonary fibrosis. Chemotherapy courses ranged between 3 and 10 (average 6), without significant differences in the two treated groups. The average dose of BCNU was 1290 mg/m^2 in the ambroxol treated group and 1300 mg/m^2 in the control group. Six patients were excluded because of post-operative severe morbidity. Of 34 evaluable patients, 18 were treated with ambroxol and 16 with placebo. The average age of patients was 56 years (range 24–67). In two cases ambroxol doses were reduced because of the appearance of skin rashes. In both groups of patients, the average number of pulmonary functional examinations was 6. Table 2 reports the results of pulmonary functional examinations as a percentage of reduction, referred to the basal values (T_0). Figures 1, 2 and 3 report the functional respiratory parameters-trend of DLCO, MMEF and MEF 25% which show a significant decrease in the control group ($P < 0.01$), in comparison to the ambroxol-treated group. No other significant variation on respiratory parameters was observed.

DISCUSSION

Selker *et al.* reported an overall incidence of 14% of symptomatic pulmonary toxicity in patients treated with nitrosourea derivatives [9]. Durant *et al.* reported a lower incidence of pulmonary fibrosis

Table 2. Results of functional respiratory parameters expressed as % of variation as compared to basal control (T_0)

Respiratory parameters		T_0	T_3	T_4	T_5	T_6
MMEF	Ambroxol	−0.85	−13.7	−5.9	−4.2	−4.9
	S.E.	6.78	4.87	5.33	4.19	4.02
	Placebo	−15.8	−23.1	−26.0*	−30.2†	−38.9†
	S.E.	7.22	8.13	7.20	6.89	6.50
MEF 25%	Ambroxol	+6.60	−7.2	−13.3	−3.1	−5.1
	S.E.	9.53	6.83	8.23	6.50	5.63
	Placebo	−9.70	−29.8*	−34.9*	−38.8†	−45.5†
	S.E.	7.57	6.27	6.99	6.62	5.28
D_LCO	Ambroxol	−25.8	−33.9	−32.5	−30.0	−28.4
	S.E.	3.15	4.54	3.87	3.86	3.53
	Placebo	−21.5	−32.5	−41.9	−41.6	−52.1†
	S.E.	6.17	5.04	4.51	4.91	4.25
FEV 1	Ambroxol	−7.31	−18.0	−15.5	−18.6	−18.0
	S.E.	3.82	4.90	3.84	4.55	6.00
	Placebo	−12.7	−17.9	−19.2	−22.0	−23.7
	S.E.	6.12	6.46	5.63	7.33	9.51
FEV 1%	Ambroxol	+9.7	+5.2	+3.13	+12.8	+12.5
	S.E.	1.68	4.11	4.26	5.80	2.5
	Placebo	−0.2	−4.1	−2.0	−5.7	−12.2*
	S.E.	6.25	6.43	5.91	6.62	8.38
CV	Ambroxol	−19.23	−19.54	−15.31	−19.00	−18.62
	S.E.	4.03	3.59	2.89	2.89	2.82
	Placebo	−14.62	−17.15	−22.00	−21.46	−23.77
	S.E.	3.05	2.75	2.81	3.51	3.87

*P 0.05 between ambroxol-treated group and placebo group.
†P 0.01 between ambroxol-treated group and placebo group.
All differences evaluated with U-test (Mann–Whitney).

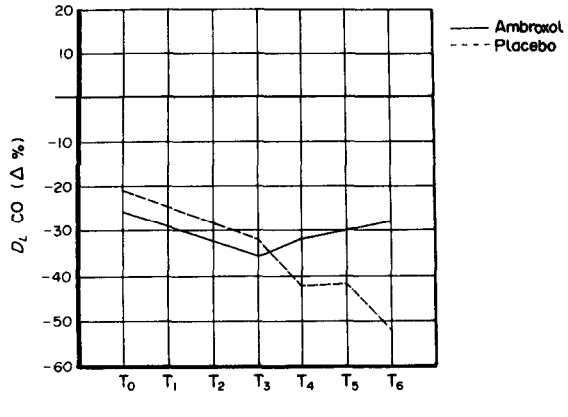

Fig. 1. DLCO-trend evaluated as % as compared to basal values (T_0).

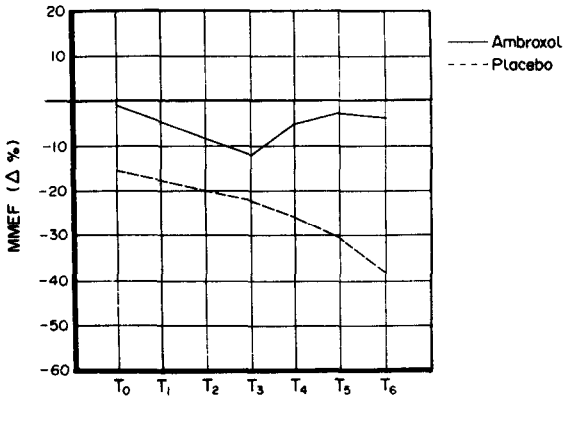

Fig. 2. MMEF-trend evaluated as % as compared to basal values (T_0).

(1.1%) in 794 patients [3]. In our previous experience, the incidence of pulmonary fibrosis in long-term administration of nitrosourea derivatives was estimated as 0.8%. The results of our investigation suggest the existence of sub-clinical lung impairment possibly evolving to major complications such as pulmonary fibrosis. In our series clinical findings and respiratory parameters in placebo-treated group are quite similar to those reported by Comis *et al.* which emphasize DLCO evaluation as an early impairment parameter of drug-induced pulmonary toxicity due to bleomycin [16]. In our patients pulmonary impairment becomes generally significant after at least 3 chemotherapy courses and depends on BCNU administered dose/m^2. Pulmonary abnormalities depend on two different fac-

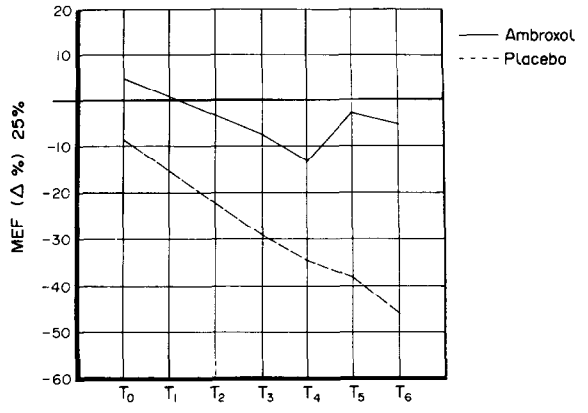

Fig. 3. MEF 25%-trend evaluated as % as compared to basal values (T_0).

tors: alveolo-capillary lesions and bronchiolar obstruction mechanism. In pulmonary fibrosis gas exchanges are abnormal because of an inhomogeneous ventilation: DLCO measurement demonstrates, in control patients treated with BCNU, a marked progressive and significant reduction ($P < 0.01$) after 5 and 6 chemotherapy courses, if compared to basal control T_0 (Fig. 1). These data suggest a reduced diffusing capacity (lower CO alveolar transport), as a typical effect of the chemotherapeutic agent on the alveolo-capillary surface. In the earlier respiratory controls (T_1–T_2) available data demonstrate a slower impairment in both groups of patients. In ambroxol-treated patients, DLCO shows an initial decrease followed by stabilization of median values (Fig. 1): this suggests the protective role of ambroxol "slowing down" the functional impairment (Table 2). On the other hand, the bronchiolar diameter is the other important feature influencing respiratory parameters, particularly MMEF and MEF 25%. In the placebo-treated group MMEF shows a significant gradual reduction. Our patients treated with ambroxol do not show the early impairment in MMEF (Fig. 2). The mechanism of ambroxol on Type II pneumocytes is commonly related to surfactant synthesis enhancement, but implies also an action on bronchiolar pathways and a marked reduction of inflammatory and immuno-effector cells [12, 17, 18], as shown in experimental models of bleomycin-induced lung disease. According to Comis and Luursema [16, 19], data regarding static respiratory parameters are not significantly different in the two groups of patients (Table 2). In our experience, also, the evaluation of MEF 25% is a sensitive parameter indicating bronchiolar obstruction (Fig. 3). In the placebo-treated group there is a significant percentage of reduction of this parameter at T_4 and T_5 (8–10 months after the beginning of chemotherapy) as compared to the ambroxol-treated patients in which the same parameter-trend could be considered in a steady-state (Fig. 3). In conclusion: DLCO, MMEF and MEF 25% are the most important respiratory parameters which have to be evaluated in patients undergoing chemotherapy with nitrosourea derivatives with the aim to detect and prevent sub-clinical pulmonary toxicity. In our series no cases of pulmonary fibrosis is shown, either in the placebo group, or in the ambroxol-treated group, but in the latter group there is no significant variation in functional parameters: these results suggest the role of ambroxol against pulmonary changes induced by long-term administration of nitrosourea derivatives.

REFERENCES

1. Paoletti P, Butti G, Casotto A, *et al.* Italian multicenter study on malignant brain tumor therapy. In: Paoletti P, Walker MD, Butti G, Knerich R, eds. *Multidisciplinary Aspects of Brain Tumor Therapy.* Amsterdam, Elsevier/North Holland, 1979, 275–282.
2. Robustelli Della Cuna G, Paoletti P, Bernardo G, Knerich R, Butti G, Cuzzoni Q. Clinical toxicity of combined modality treatment with nitrosourea derivatives for central nervous system tumors. *Neurosurgery* 1982, **11**, 408–411.
3. Durant JR, Norgard MJ, Murad TM, Bartolucci AA, Langford KH. Pulmonary toxicity associated with bischloroethylnitrosourea (BCNU). *Ann Intern Med* 1979, **90**, 191–194.
4. Hasleton PS. Busulfan lung: histopathology. *Thorax* 1970, **25**, 257.
5. Saunier C. Fibroses pulmonaires interstitielles expérimentales. *Bull Europ Physiopath Resp* 1982, **18**, 515–547.
6. Johnson KJ, Fantone JC III, Kaplan J, Ward PA. *In vivo* damage of rat lungs by oxygen metabolites. *J Clin Invest* 1981, **67**, 983–993.
7. Thrall RS, McCormick JR, Jack RM, McReynolds RA, Ward PA. Bleomycin-induced pulmonary fibrosis in the rat. Inhibition by indomethacin. *Am J Pathol* 1979, **95**, 117–127.
8. Rosenow EC III. The spectrum of drug-induced pulmonary disease. *Ann Intern Med* 1972, **77**, 977–991.
9. Selker RG, Jacobs SA, Moore PB, *et al.* 1,3-*bis* (chloroethyl)-1-nitrosourea (BCNU)-induced pulmonary fibrosis. *Neurosurgery* 1980, **7**, 560–565.
10. Holoye PY, Jenkins DE, Greenberg SD. Pulmonary toxicity in long-term administration of BCNU. *Cancer Treat Rep* 1976, **60**, 1691–1694.
11. Iriarte PV, Hananian J, Cortner JA. Central nervous system leukemia and solid tumors of childhood. Treatment with 1,3-*bis* (chloroethyl)-1-nitrosourea (BCNU). *Cancer* 1966, **19**, 1187–1194.

12. Curti PC, Steigerung der Produktion der doerflachenaktiven Substanz der Alveolen dur NA 872. *Pneumologie* 1972, **147**, 62–74.
13. Pozzi E, Zanon P. On the pathogenesis of bleomycin lung toxicity. *Int J Clin Pharmacol* 1978, **16**, 575–578.
14. Ogilvie CM, Forster RE, Blakemore WS, Morton JW. A standardized breath holding technique for the clinical measurement of the diffusing capacity of the lung for carbon monoxide. *J Clin Invest* 1957, **36**, 1–17.
15. Butti G, Knerich R, Tanghetti B, *et al.* Preoperative carmustine (BCNU) chemotherapy for malignant brain tumors. *Cancer Treat Rep* 1984, **68**, 1505–1506.
16. Comis RL, Kuppinger MS, Ginsberg SJ, *et al.* Role of single-breath carbon monoxide-diffusing capacity in monitoring the pulmonary effects of bleomycin in germ cell tumor patients. *Cancer Res* 1979, **39**, 5076–5080.
17. Grassi C, Luisetti M, De Rose V, *et al.* Biomedical and functional changes in bronchoalveolar parameters induced by ambroxol treatment of chronic bronchitis. In: Cosmi EV, Scarpelli EM, eds. *Pulmonary Surfactant System.* Amsterdam, Elsevier, 1983, 361–370.
18. Luisetti M, Peona V, Salmona M, *et al.* Ambroxol and pulmonary toxicity induced by antineoplastic drugs. *Int J Clin Pharmacological Res* 1986, **6**, (Supp. 1), 129–136.
19. Luursema PB, Star-Kroesen MA, Van der Mark ThW, Sleyfer DT, Schraffordt Koops H, Peset R. Bleomycin-induced changes in the carbon monoxide transfer factor of the lungs and its components. *Am Rev Respir Dis* 1983, **128**, 880–883.