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Short Communications

High-Dose Methotrexate with Citrovorum Factor Rescue in Non-Small-Cell Lung Cancer

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Summary. *Nineteen patients with non-small-cell carcinoma of the lung were treated with high-dose methotrexate and leucovorin rescue. Two partial responses (10.5%) were observed, lasting 13 and 17 weeks. Toxicity was acceptable. It is concluded that the occasional benefit of high-dose methotrexate with leucovorin rescue at this dose and according to the schedule described for these patients does not warrant further study.*

Introduction

Patients with unresectable or recurrent carcinoma of the lung have a dismal prognosis, accounting for 280 deaths per day in the United States [1, 5]. Only 10% of the patients are curable surgically at the time of diagnosis, the remaining 90% requiring nonsurgical therapy at some point during their life-span [1]. Although the medical treatment of small-cell lung cancer has improved significantly over the past few years [3, 11], various approaches utilizing surgery, radiotherapy, chemotherapy, or combinations thereof have achieved little success in the treatment of other histologic types (epidermoid, adenocarcinoma, and large-cell anaplastic carcinoma). Response rates have stayed uniformly below 35%–40%, with responders living only a few months longer than nonresponders [8, 15, 17]. On the basis of the published studies demonstrating that some tumors insensitive to conventional doses of methotrexate can regress with higher doses of the drug followed by citrovorum factor rescue [2, 3, 6, 9, 12] and some early encouraging data suggesting that responses may be achieved in various types of bronchogenic carcinoma [7], a pilot study was done to evaluate the efficacy of high-dose methotrexate with citrovorum factor rescue in patients with advanced non-small-cell lung cancer.

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Materials and Methods

Nineteen patients from Vanderbilt University Hospital and Nashville Veterans Administration Hospital were entered on the study. All patients had unresectable tumors with measurable lesions, and 14 had received no prior radiation or chemotherapy. There were 17 male and 2 female patients, their ages ranging from 37–63 years. All patients were ambulatory, with a functional status of above 70 on the Karnofsky scale. Histologic types were squamous-cell carcinoma (6 patients), adenocarcinoma (8 patients), and large-cell anaplastic carcinoma (5 patients). All patients were investigated to define the extent of disease with history, physical examination, chest X-ray, CBC, liver functions (SGOT, SGPT, bilirubin, alkaline phosphatase), calcium, BUN, creatinine, and brain, bone, and liver scans if clinically indicated. All patients had 24-h urine creatinine clearances of above 50 ml/min and an expected life-span of longer than 2 months. Patients with active skin rashes, infections, or large effusions were not included.

Patients were treated at the Clinical Research Center at Vanderbilt University Hospital. They were hydrated 12 h prior to therapy, usually with intravenous (IV) half-normal saline 3000 ml/m^2/24 h containing 240 mEq $NaHCO_3$/m^2/24 h and 60 mEq KCl/m^2/24 h to achieve an alkaline (pH $\geq$ 7) urine output of more than 100 ml/h. Vincristine 2 mg IV push was given before the methotrexate, in an attempt to increase intracellular methotrexate [10]. This was followed in one hour by 6–10 g methotrexate/m^2 infused over 6 h[1]. Two hours after the infusion was finished, rescue was started with 15 mg leucovorin/m^2 IM every 6 h for 12 doses. Urine output > 100 ml/h and pH $\geq$ 7 was maintained with additional $NaHCO_3$ and furosemide as necessary. Methotrexate levels were determined by means of a competitive binding assay [14]. If 48-h methotrexate levels were less than 5×10^{-7} *M*, leucovorin was discontinued after 12 doses. If not, leucovorin rescue was increased and continued until the plasma methotrexate levels were less than 1×10^{-8} *M* [16]. Patients were observed carefully for toxicity, with particular attention to renal function, skin, and mucous membranes. Response was assessed at the end of three cycles unless patients showed evidence for progression. Partial response was defined as a 50% or more reduction in the products of the two longest dimensions of the measurable mass lesion.

The first 11 patients were treated every 3 weeks. Upon evaluation of the response rate and toxicity at that point, the cycle length was reduced to 1 week, and eight more patients were treated with weekly methotrexate.

[1] Methotrexate and leucovorin supplied by the Division of Cancer Treatment, National Cancer Institute

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Results

Among the 11 patients treated every 3 weeks, there was one partial response of 17 weeks' duration (Table 1). This patient had an adenocarcinoma of the lung with a measurable pulmonary lesion and carcinomatous leptomeningitis. She had a partial response as measured by chest X-ray, and malignant cells were cleared from her cerebrospinal fluid. Methotrexate levels in the cerebrospinal fluid were in the therapeutic range (1×10^{-7} *M* at 60 h post infusion).

Eight patients were started on treatment initially with the weekly schedule, with one partial response continuing for 13 weeks being observed (Table 2). Three patients who failed the 3-weekly schedule were tried on weekly therapy, and none responded. The median survival time for the groups (16 patients) was 53 weeks. The two responders survived for 36+ and 32+ weeks.

Nineteen patients received 80 cycles of therapy. Two of the 80 cycles (2.5%) in two patients were associated with myelosuppression and stomatitis (48-h methotrexate levels were less than 5×10^{-7} *M*). No serious complications were observed in the other patients. Specifically, they did not experience myelosuppression, mucositis, skin rash, nephrotoxicity, or permanent liver damage. Four patients had transient elevations of their serum transaminase levels. Patient compliance was satisfactory, and difficulties were related more to the inconvenience of hospitalization rather than drug toxicity.

Discussion

Although high-dose methotrexate with leucovorin rescue and vincristine was tolerated well by our patients, the

Table 1. Patient characteristics and response to high-dose methotrexate given every 3 weeks in non-small-cell lung carcinoma

	Age/Sex	Histology	Disease site	Response	Number of cycles	Toxicity
1.	54/M	Large cell	Chest, bone	None	5	None
2.	45/M	Large cell	Chest	None	3	None
3.	63/F	Adenocarcinoma	Chest, nodes, meninges	PR[a]	5	None
4.	42/M	Adenocarcinoma	Chest, liver	None	3	None
5.	48/M	Adenocarcinoma	Chest, bone	None	3	None
6.	41/M	Adenocarcinoma	Chest, liver, skin	None	3	None
7.	53/F	Squamous cell	Chest	None	5	None
8.	45/M	Adenocarcinoma	Chest, bone	None	2	None
9.	37/M	Large cell	Chest	None	3	None
10.	56/M	Squamous cell	Chest, bone	None	3	None
11.	60/M	Squamous cell	Chest, bone	None	2	Myelosuppression

[a] Duration of response, 17 weeks

Table 2. Patient characteristics and response to high-dose methotrexate given weekly in non-small-cell lung carcinoma

	Age/Sex	Histology	Previous MTX	Disease site	Response	Number of cycles	Toxicity
1.	54/M	Large cell	Every 3 weeks	Chest, bone	None	4	None
2.	63/F	Adenocarcinoma	Every 3 weeks	Chest, bone, meninges	None	4	None
3.	53/F	Squamous cell	Every 3 weeks	Chest	None	5	None
4.	58/M	Squamous cell	None	Chest, bone	None	6	None
5.	62/M	Adenocarcinoma	None	Chest, nodes	None	3	None
6.	40/M	Adenocarcinoma	None	Chest, nodes	None	3	None
7.	46/M	Large cell	None	Chest	None	3	None
8.	53/M	Squamous cell	None	Chest	None	2	None
9.	55/M	Adenocarcinoma	None	Chest	None	3	None
10.	58/M	Large cell	None	Chest	PR[a]	6	None
11.	56/M	Squamous cell	None	Chest, nodes	None	3	Stomatitis and myelosuppression

[a] Duration of response, 13 weeks

response rate was low and the duration of these responses short. Similar results have been reported by other investigators [13]. We believe the occasional benefit of high-dose methotrexate at the doses and according to the schedules employed in this study for these patients does not justify the inconvenience and cost of further trials with this regimen.

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References

1. American Cancer Society: Cancer Facts and Figures. New York: American Cancer Society 1978
2. Bertino, J. R.: "Rescue" techniques in cancer chemotherapy: Use of leucovorin and other rescue agents after methotrexate treatment. Semin. Oncol. **4,** 203 (1977)
3. Bunn, P. A., Cohen, M. H., Ihde, D. C., Fossieck, B. E., Matthews, M. J., Minna, J. D.: Advances in small cell bronchogenic carcinoma. Cancer Treat. Rep. **61,** 333 (1977)
4. Capizzi, R. L., DeConti, R. C., Marsh, J. C., Bertino, J. R.: Methotrexate therapy of head and neck cancer: Improvements in therapeutic index by the use of leucovorin "rescue". Cancer Res. **30,** 1782 (1970)
5. Cutler, S. J., Young, J. L.: Third National Cancer Survey: Incidence data. Natl. Cancer Inst. Monogr. **41,** 1 (1975)
6. Djerassi, I.: High-dose methotrexate (NSC0740) and citrovorum factor (NSC-3590) rescue: Background and rationale. Cancer Chemother. Rep. (Part 3) **6,** 3 (1975)
7. Djerassi, I., Rominger, C. J., Kim, J. S., Turchi, J., Suvansri, V., Highes, D.: Phase I study of methotrexate with citrovorum factor in patients with lung cancer. Cancer **30,** 22 (1972)
8. Eagan, R. T., Ingle, J. N., Frytak, S., Rubin, J., Kvols, L. K., Carr, D. T., Coles, D. T., O'Fallon, J. R.: Platinum-based polychemotherapy versus dianhydrogalactilol in advanced non-small-cell lung cancer. Cancer Treat. Rep. **61,** 1339 (1977)
9. Goldin, A., Mantel, N., Greenhouse, S. W., Venditti, J. M., Humphreys, S. R.: Estimation of the antileukemia potency of antimetabolite aminopterin administered alone and in combination with citrovorum factor or Folic acid. Cancer Res. **13,** 843 (1953)
10. Goldman, I. D., Fyfe, M.: Mechanism of Action of Methotrexate II. Augmentation by vincristine of inhibition of deoxyribonucleic acid synthesis by methotrexate in Ehrlich ascites tumor cells. Mol. Pharmacol. **10,** 275 (1974)
11. Greco, F. A., Richardson, R. L., Schulman, S. F., Stroup, S., Oldham, R. K.: Treatment of oat cell carcinoma of the lung: complete remissions, acceptable complications and improved survival. Br. Med. J. **1978 II,** 10
12. Jaffe, N., Frei, E., III, Traggis, D., Bishop, Y.: Adjuvant methotrexate and citrovorum factor treatment of osteogenic sarcoma. N. Engl. J. Med. **291,** 994 (1975)
13. Minna, J., Pelsor, F., Ihde, D., Bunn, P., Gazdar, A., Cohen, M.: High-dose methotrexate therapy by 6- or 30-hour infusion with leucovorin rescue in non-small lung cancer. Proc. Amer. Ass. Cancer Res. **19,** 135 (1978)
14. Myers, C. E., Lippman, M., Eliot, H. M., Chabner, B. S.: Competitive protein binding assay for methotrexate. Proc. Natl. Acad. Sci. USA **72,** 3683 (1975)
15. Selawry, O. S.: Polychemotherapy with adriamycin (NSC-123127) in bronchogenic carcinoma. Cancer Chemother. Rep. (Part 3) **6,** 353 (1975)
16. Selawry, O. S., Primack, A. (eds.): First International Workshop for Therapy of Lung Cancer. Cancer Chemother. Rep. (Suppl.) **4,** 2 (1973)
17. Stoller, R. G., Hande, K. R., Jacobs, S. A., Rosenberg, S. A., Chabner, B. A.: Use of plasma pharmacokinetics to predict and prevent methotrexate toxicity. N. Engl. J. Med. **297,** 630 (1977)

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