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# Combination Chemotherapy (High-Dose Methotrexate with Citrovorum Factor Rescue, Mechlorethamine, and Procarbazine) in Non-Small Cell Lung Cancer

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***Summary.*** *Twenty-five patients with non-small cell lung cancer (NSCLC) were treated with high-dose methotrexate with citrovorum factor resuce (HDMTX-CFR), mechlorethamine ($HN_2$) and procarbazine (PCZ). Nineteen patients are evaluable for response. One patient had partial remission which lasted for 11 weeks. Nine patients had stable disease lasting for 6–22 weeks. HDMTX-CFR was well tolerated by these patients but this combination regimen produced very low tumor response rate (5.2%). Addition of $HN_2$ and PCZ, chemotherapeutic agents active against NSCLC, failed to improve the tumor response rate but added to gastrointestinal and hematologic toxicity.*

## Introduction

The prognosis of patients with advanced non-small cell lung cancer (NSCLC) remains dismal. Single-agent therapy with mechlorethamine ($HN_2$), methotrexate (MTX), or procarbazine (PCZ) has yielded objective response rates of 18%–36% with no significant impact on survival [9, 10]. Combinations of methotrexate, procarbazine, cyclophosphamide, and doxorubicin have produced response rates of 31% with improved survival for responders [1, 8]. High-dose MTX (HDMTX) with citrovorum factor resue (CFR) is reported to have an increased therapeutic index in tumors relatively resistant to conventional-dose MTX [2, 3, 6]. On the basis of these reports, we decided to examine a combination of HDMTX with CFR and two other agents with activity against NSCLC, $HN_2$ and PCZ.

## Materials and Methods

Twenty-five patients with advanced NSCLC previously untreated with chemotherapy were admitted to M.D. Anderson Hospital, Houston, Texas, USA, and entered on the study. Six patients are inevaluable for response, for the following reasons: lost to follow-up after receiving the first course of chemotherapy (3 patients), death within 2 weeks of entry on the study (2 patients), and a subsequent bone marrow biopsy which changed the diagnosis to oat cell lung cancer (1 patient). Data from 19 patients were analyzed.

All patients were ambulatory and had creatinine clearance of $\geq$ 60 ml/min. Patients were started on hydration at least 12 h prior to MTX infusion with IV 0.5 N saline at the rate of $\geq$ 2,500 ml/m$^2$/24 h. Hydration was continued until completion of CFR. Urine pH was maintained at $\geq$ 7.0 by addition of sodium bicarbonate PO or IV. On day 1 of the treatment cycle, MTX (1,500 mg/m$^2$) was infused over 6 h. Four hours after completion of MTX infusion, CFR was given in doses of 7.5 mg/m$^2$ every 6 h IV or PO until the plasma MTX level was less than $5 \times 10^{-7}$ *M*. Plasma MTX level was measured by an enzymatic competitive binding assay at 24 and 48 h. If the 48-h plasma MTX level was more than $5 \times 10^{-7}$ *M*, hydration and alkalinization were continued and the CFR dose was increased until the plasma MTX level was less than $1 \times 10^{-8}$ *M*. $HN_2$ was given in doses of 7.5 mg/m$^2$ on days 1 and 2, as an IV push through a running IV infusion; PCZ was given PO in doses of 100 mg/m$^2$ daily for 10–14 days.

Chemotherapy courses were repeated at 3- to 4-week intervals. Response was assessed on completion of two cycles to treatment, but a definite progression of disease after the first cycle of treatment was counted as progression.

We defined complete response (CR) as the complete disappearance of all clinically detectable tumor; partial response (PR), as $\geq$ 50% reduction in the product of the two longest dimensions of the measurable lesion for 6 weeks or more; stable disease (SD), as $<$ 50% reduction in the measurable lesion for 6 weeks or more with no progression; and progressive disease (PD), as the appearance of new metastases or a $>$ 25% increase in pre-existing lesions.

## Results

Nineteen patients are evaluable for response (Table 1). Seventeen patients were male and two female, with ages varying from 40 to 69 years. Five patients had adenocarcinoma, five squamous, four poorly differentiated, three large cell, and two adenosquamous carcinomas. One patient had PR lasting for 11 weeks. This 54-year-old male patient had poorly differentiated NSCLC in the lung and bilateral cervical and supraclavicular lymph nodes. Partial remission was noted in the neck nodes after the first cycle of treatment. All neck nodes disappeared after the third cycle of treatment and the right lung infiltrate improved ($<$ 50%). After 11 weeks of PR, progression was noted in the lung and pleurae, and later in the neck nodes. Nine patients had SD for 6–22 weeks. The median survival of all evaluable patients is 22 weeks. The median survival of patients with PR or SD was 23 weeks, as against 11 weeks for non-responders ($P > 0.05$).

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**Table 1.** Patient and disease characteristics

| No. | Initials | Age (years) | Sex | Histology | Site of disease | Response[a] | Site of progression or response | Number of treatment cycles | Survival (weeks) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | W.M. | 54 | M | Adenocarcinoma | Lung, lymph nodes | SD | | 6 | 23 |
| 2 | L.T. | 43 | M | Adenocarcinoma | Lungs | SD | | 5 | 33 |
| 3 | B.S. | 58 | M | Large cell | Pleura, mediastinum | SD | | 4 | 32 |
| 4 | A.S. | 59 | M | Poorly diff. | Pleura, mediastinum, para-aortic nodes | SD | | 4 | 22 |
| 5 | J.J. | 64 | M | Squamous | Lung, lymph nodes | SD | | 4 | 45 |
| 6 | W.P. | 54 | M | Poorly diff. | Lung, lymph nodes | PR | Lymph nodes | 4 | 26 |
| 7 | K.C.J. | 65 | M | Squamous | Lungs | SD | | 3 | 33 |
| 8 | E.U. | 66 | M | Adenosquamous | Lung, lymph nodes | SD | | 3 | 14 |
| 9 | N.E. | 48 | F | Large cell | Lung, soft tissue | SD | | 3 | 22 |
| 10 | D.H. | 42 | M | Large cell | Lung, soft tissue | PD | Soft tissue | 3 | 63 |
| 11 | J.T. | 53 | M | Squamous | Lung, mediastinum | PD | Lung, mediastinum | 2 | 5+ |
| 12 | A.B. | 40 | M | Adenocarcinoma | Lung, pericardium | PD | Pericardium | 2 | 60 |
| 13 | G.C. | 60 | M | Poorly diff. | Lung, pleura | PD | Lung, bone | 2 | 11 |
| 14 | J.P. | 57 | F | Squamous | Lung, lymph nodes, liver | SD | | 2 | 6 |
| 15 | A.L. | 48 | M | Adenocarcinoma | Bone, lymph nodes, pleura | PD | Bone | 1 | 8 |
| 16 | A.G. | 69 | M | Poorly diff. | Lymph nodes, liver, bone, skin | PD | Liver | 1 | 4 |
| 17 | C.H. | 47 | M | Squamous | Lung, abdominal wall, CNS | PD | Lung | 1 | 26 |
| 18 | A.J.T. | 50 | M | Adenocarcinoma | Lymph nodes, soft tissue | PD | Soft tissue | 1 | 9 |
| 19 | J.L. | 57 | M | Adenosquamous | Lungs, CNS | PD | Lung | 1 | 18 |

[a] Response assessed on completion of two treatment cycles unless definite progression noted after one treatment cycle: SD, stable disease; PR, partial remission; PD, progressive disease

Fifty-two cycles were evaluated for toxicity. Nausea, vomiting (44 cycles), and diarrhea (16 cycles) occurred mainly after IV injections of $HN_2$. Hematologic toxicity was mainly related to PCZ and $HN_2$ and required reduction of PCZ dose in many cycles. Nadir platelet counts of $< 50{,}000/mm^3$ were noted in 20 cycles. Six cycles were complicated by minor bleeding, which was manifested as petechiae, bleeding gums, or mild epistaxis. Nadir white cell count of $< 500/mm^3$ occurred in three cycles. Two patients had three episodes of fever and one patient had left lower lobe pneumonia in two cycles. No renal toxicity was noted. Other toxicities noted were: stomatitis (1 cycle) and skin rash (2 cycles). We found no significant correlation between any type or grade of toxicity and 24- or 48-h plasma MTX level.

## Discussion

Controversial results have been reported on the efficacy of HDMTX with rescue in non-small cell lung cancer [2, 4–7]. Djerassi et al. [2] reported objective responses in nine of ten patients and Isacoff et al. [6] reported one CR and five PRs in 18 patients with NSCLC. Subsequent studies [4, 5, 7] have reported response rates of 4%–10%. The response rate of 5% achieved in our study is in keeping with the latter studies. It is concluded that HDMTX is well tolerated by elderly patients, but that the tumor response rate is low. Addition of two chemotherapeutic agents active against NSCLC, $HN_2$ and PCZ, failed to improve the tumor response rate but added to gastrointestinal and hematologic toxicities.

## References


1. Bitran JD, Desser RK, DeMesster T, Golomb HM (1978) Metastatic non-oat cell bronchogenic carcinoma. Therapy with cyclophosphamide, doxorubicin, methotrexate and procarbazine (CAMP). JAMA 240: 2743
2. Djerrassi I, Rominger CJ, Kim JS, Turchi J, Suvansri V, Highes D (1972) Phase I study of high doses of methotrexate with citrovorum factor in patients with lung cancer. Cancer 30: 22
3. Djerassi I, Kim JS, Ohanissian H (1978) High-dose methotrexate (HDMTX) and citrovorum factor rescue (CFR) in solid tumors. Chemisterapia Oncologica [suppl 2] 4: 243
4. Ettinger DS, Stanley DE, Nystrom JS (1980) Phase II study of patients with non-small cell carcinoma of the lung: An eastern cooperative oncology group study. Cancer Treat Rep 64: 1017
5. Greco FA, Fer MF, Richardson RL, Hande KR, Van Boxtel CJ, Oldham RK (1978) High-dose methotrexate with citrovorum factor rescue in non-small cell lung cancer. Cancer Chemother Pharmacol 1: 255
6. Isacoff WH, Eilber F, Tabbarah H, Klein P, Dollinger M, Lemkin S, Sheehy P, Cone L, Rosenbloom B, Sieger L, Block JB (1978) Phase II clinical trial with high-dose methotrexate therapy and citrovorum factor rescue. Cancer Treat Rep 62: 1295
7. Minna J, Pelsor F, Ihde D, Bunn P, Gazdar A, Cohen M (1978) High-dose methotrexate (HDMTX) therapy by 6- or 30-hour infusion with leucovorin rescue (LR) in non-small cell lung cancer. Proc AACR/ASCO 19: 135
8. Volgelzang JH, Bonomi PD, Rossof AH, Wolter J (1978) Cyclophosphamide, adriamycin, methotrexate and procarbazine (CAMP) treatment of non-oat cell bronchogenic carcinoma. Cancer Treat Rep 62: 1595
9. Samuels ML, Leary WV, Howe CD (1969) Procarbazine (NSC-77213) in the treatment of advanced bronchogenic carcinoma. Cancer Chemother Rep 53: 135–145
10. Selawry OS (1973) Monochemotherapy of bronchogenic carcinoma with special reference to cell type. Cancer Chemother Rep 4: 177–188


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