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CLINICAL INVESTIGATION STUDY PROTOCOL

MED-6000-3

INSTITUTION: Naval Regional Medical Center, Portsmouth, Virginia 23708

TITLE: Chemoimmunotherapy of Carcinoma of the Lung using High Dose Methotrexate and BCG

INVESTIGATORS:

NAV1.954256.002

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Percent of time available for study - 10%
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A. OBJECTIVES:

1. To evaluate the response of Carcinoma of the Lung to Chemotherapy with High e Methotrexate - Citrovorum Rescue.

2. To further evaluate the effect of BCG in Carcinoma of the Lung as regards both clinical response and immunologic function.

3. To function as a pilot study for the eventual use of Chemoimmunotherapy as an adjuvant to post thoracotomy patients with no residual tumors.

B. BACKGROUND:

In spite of intense efforts in the fields of surgery, radiation, and chemotherapy three year survival rates in lung cancer remain dismally low at about 5%. Immunotherapy has shown some promise in the therapy of certain human malignancies, most recently in lung cancer as a result of studies done at Naval Hospital Portsmouth and other cooperating institutions. In this study initiated in June 1974 lung cancer patients with minimum residual disease had a significantly lower relapse rate when given BCG than did matched controls. Immunotherapy is safe and has low toxicity in comparison to standard methods of treatment of lung cancer. Further trials of immunotherapy in humans, therefore, seem warranted.

Encl (99)

Methotrexate as a single agent produces objective regression rates ranging from 12% to 39% in all histologic types of lung cancer. Dr. Isaac Djerassi (Philadelphia) has used high dose methotrexate with citrovorum rescue in lung cancer since 1972 and has provided evidence of enhanced response with this method such that it compares favorably both in toxicity and in response rate to any other chemotherapy regimen.

In view of the foregoing it would seem reasonable to combine methotrexate rescue and BCG in an attempt to treat lung cancer. It is proposed that a cooperative effort be undertaken by three institutions, Naval Hospital Portsmouth, National Cancer Institute, and Walter Reed Army Medical Center to study the efficacy of methotrexate rescue with and without BCG immunotherapy in treatment of selected patients with lung cancer. The formal proposal is attached(enclosure 1) and has been accepted in principle by NCI and by Walter Reed Army Medical Center. Approximately 12 patients annually can be entered from Naval Hospital Portsmouth and another 12 from the other two institutions. It is estimated that the protocol will need to remain open to entry for one to three years.

C. APPROACH:

Patients with biopsy proved lung cancer confined to the thorax will be eligible. An explanation of the experimental nature of the proceedure, toxicity, possible complications, and expected benefit will be given to all eligible patients. Consenting patients will be asked to sign an appropriate consent form (enclosure 2) and then will be randomized to one or the other arms (high dose MTX with or without BCG) of the protocol. Clinical parameters will be objective change in tumor size, length of disease free interval, survival, and clinical and laboratory toxicity date. Immunologic parameters followed will be skin reaction to recall antigens, LMI, lymphocyte rosettes, PHA & MLC. Methotrexate serum levels will be assayed by the I125 MIA technique.

Data will be analysed every 3 months and appropriate changes made in the protocol.

10.0 Study parameters

Study	Weekly	Before each cycle of MTX[a] or radiation	Every 2 cycles	Every 3 mos. befor inception of following cycle
CBC with platelet count	X			
SMA 12/60 and 6/60		X		
Creatinine		X		
Creatinine clearance			X[a]	
Chest film - PA & lateral			X	
CEA			X	
H & P with measurements of lesions & determination of Karnovsky rating		X[b]		
Skin tests - recall & tumor assoc. antigens				X
KLH skin test		X[b]		
4° & 29° Rosettes (10ml)		X[c]		
Lymphocyte migration stimulation (40ml)		X[c]		
Lymphocyte proliferation (10ml)		X[c]		
10cc serum bank specimen				X
Serum MTX levels		X[d]		

[a]Patients on high dose MTX with or without BCG - every 2 cycles
[b]Serum drawn at time 0 and injection of 2.5mg of KLH given, then serum and skin tests done at 1,2,3,6 months and then at 3 month intervals
[c]To be drawn before inception of each chemotherapy cycle
[d]72 hours after start of MTX infusion

10.1 Skin tests will be done every three months. Patients will be tested with PPD (5 T.U.), SKSD (40 U), and will also be tested with Hollinshead extracts derived from CaLu--a tissue culture line derived from pulmonary adenocarcinoma. These same tumor extracts will be simultaneously used in LMI. KLH skin testing will be done on the schedule given in footnote c.
10.2 A total of 60 ml of whole blood will be drawn into preservative free heparin for use in the immunologic assays. 10 ml will be used for rosette determinations. 40 ml will be used for LMI with PPD and purified extracts of CaLu as described in 10.1. 10 ml will be used for lymphocyte proliferation with PHA and in MLC. Blood will be drawn immediately before the inception of chemotherapy and will be forwarded to Litton Bionetics where these procedures will be performed.
10.3 10 ml of serum will be collected every three months before the chemotherapy cycle and will be kept at -70° C at the LRI for future testing.
10.4 MTX levels will be determined as described in section 9.16.

11.0 Off study criteria
11.1 Patients receiving high dose MTX will not be considered to have progressive disease until four cycles of chemotherapy of at least 200mg/kg have been completed.