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PHASE I TRIAL OF ETOPOSIDE AND CISPLATIN PLUS CHEST RADIOTHERAPY FOR PATIENTS WITH LIMITED STAGE SMALL CELL LUNG CANCER

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1 Precis

This is a Phase I trial of a 12-21 day course of oral etoposide plus cisplatin with BID chest radiotherapy for patients with untreated limited stage small cell lung cancer (SCLC). Patients will be treated with increasing doses of oral etoposide until the maximum tolerated dose of etoposide cisplatin with a concurrent course of chest radiotherapy at a dose of 45 Gy is determined. Then the dose of chest radiotherapy will be escalated to determine the maximal tolerated dose of chest radiation. After completion of the concurrent combined modality therapy, patients will be treated with cyclophosphamide, doxorubicin, and etoposide alternating with etoposide cisplatin for a total of six months of therapy. In addition to the concurrent treatment, patients will be offered the opportunity to undergo a biopsy to have their tumor tissue studied for the presence of p53 gene mutations. If the patients have a p53 mutation and relapse with small cell lung cancer, they will be offered the opportunity to participate in a previously approved protocol (MB-272) studying the vaccination of patients with mutated p53 peptide incubated with their own lymphocytes.

2 SCHEMA

WEEK	
0	Staging investigations and tissue procurement
1	Etoposide orally days 1 through 12 or 21 Cisplatin administration day 1
1-3	Chest Radiotherapy
5	Repeat etoposide and cisplatin
8	CAVP-16
11	Repeat etoposide cisplatin
15	Repeat CAVP-16
18	Repeat etoposide cisplatin
22	Repeat CAVP-16
25	Restage and administer prophylactic cranial irradiation if patients are in complete response.

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3 INTRODUCTION AND RATIONALE

3.1 Introduction

The response rate of patients with limited stage small cell lung cancer to combined modality therapy (chest radiotherapy plus chemotherapy) is 70-90% Despite these high response rates, the five-year survival of patients with limited stage small cell lung cancer is only 4-17% (1-3). Recent attempts to increase the therapeutic efficacy and reduce the morbidity and mortality of combined modality regimens have included the use of etoposide and cisplatin concurrently with chest radiotherapy (4), administering the chest radiotherapy in two daily fractions instead of a single dose (5-7), and giving the chest radiotherapy interspersed between the chemotherapy cycles (alternating therapy) (8,9). These have resulted in median survivals of 18-27 months and 2-year survival rates of 35-65% (4-7,10). However, the survival at 3-5 years remains at only 20-40% (4,6,11) so more effective therapy is needed. Therefore, we propose use a Phase I format to incorporate the administration of cisplatin plus a 12-21 day course of increasing duration and dosage of etoposide. After the maximum tolerated dose of etoposide cisplatin is established, increasing doses of twice daily chest radiotherapy will be administered. In addition, after two cycles of etoposide cisplatin, we will alternate it with the regimen cyclophosphamide, doxorubicin, and etoposide for a total of six months of therapy.

In addition to these outlined studies, we will also make an attempt to biopsy the patients to obtain tumor tissue. The tumor tissue will be used to sequence the potential p53 mutation which is present in nearly 80% of patients with small cell lung cancer (12-14). If a mutation is present, an attempt to treat the patients at the time of relapse with a custom synthesized peptide which contains the mutation of their p53 gene. This will be done by incubating a synthetic peptide with the patients autologous lymphocytes as described in the previously approved clinical protocol MB-272 and in section 3.7.

3.2 Rationale for Combined Modality

Two recent meta-analyses of 11-13 prospectively randomized trials comparing chemotherapy to the same chemotherapy plus chest irradiation for patients with limited stage small cell lung cancer showed 5% more patients alive at 2 and 3 years when they were treated with combined modality therapy (15,16). In addition, a previous analysis of patients treated with a variety of combined modality regimens at the Radiation Oncology Branch showed that combined modality therapy given for 3 weeks concurrently maximized 2-year survival and

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minimized the fatal toxicity of treatment (17). This principle was applied in a randomized trial at the NCI-VA and NCI-Navy Medical Oncology branch conducted from 1977-1986 which showed patients treated with a cyclophosphamide based chemotherapy regimen and 3 weeks of chest radiotherapy lived longer than patients treated with chemotherapy alone (18). The median survival of patients treated with combined modality in this trial was 15 months and the 2-year survival was approximately 20%. However, 6 of 47 (12%) patient treated with combined modality therapy died of toxicity while in complete remission. In order to reduce the toxicity and improve the efficacy, the subsequent combined modality trial using etoposide cisplatin plus twice daily chest radiotherapy has been performed as a single arm study and has achieved a median survival of approximately 24 months and a 2-year survival of approximately 50% (6). In addition, other trials using etoposide cisplatin plus once or twice daily chest radiotherapy have achieved similar results with minimal pulmonary toxicity. A single institution study of 23 patients and cooperative group studies by the Southwest Oncology Group and National Cancer Institute of Canada of 462 patients with limited stage small cell lung cancer had no episodes of fatal pulmonary toxicity in patients treated with etoposide cisplatin with or without vincristine plus once daily chest radiotherapy (4,5,10). Therefore, it appears that the combination of etoposide cisplatin plus chest radiotherapy given once or twice daily is associated with a reduced incidence of pulmonary toxicity.

However, more than 60% of these 50 patients treated on the most recent combined modality study have relapsed with small cell lung cancer. Therefore, we would like to continue to use the combined modality therapy but attempt to improve both the local control by increasing the dose of chest radiotherapy as well as the systemic therapy by using a prolonged period of exposure to oral etoposide. In addition, we would like to take advantage of administering etoposide concurrently with the chest radiotherapy. We will take advantage of the previously developed prolonged regimen of oral etoposide to administer etoposide and chest radiation therapy concurrently for an extended duration.

3.3 Rationale for 12-21 Day Course of Etoposide

Etoposide is among the most active agents used in combination chemotherapy regimens for patients with small cell lung cancer (19,20) and the schedule of administration has an impact on its response rate and survival . The activity of etoposide used in different schedules against small cell lung cancer has been compared in randomized single agent and combination studies. The response rate is 67% when administered over 3-5 days compared to 15% with a single dose and the 3-5 day

regimens are associated with longer survival (21-23). A 5 day regimen of etoposide has been used as the sole treatment in 107 elderly patients with small cell lung cancer (> 70 years) in an attempt to minimize the toxicity of treatment (24,25). The overall response rate was 73% and the median survival of these patients was approximately 9 months, similar to the results achieved with conventional combination chemotherapy. Etoposide has also been shown to have antitumor activity using prolonged schedules of 14 to 21 days of therapy in single arm studies as a single agent or in combination. Patients who had previously received chemotherapy were treated with 50 mg/m^2 by mouth for 21 days (26,27). Sixteen of 48 (33%) had a complete (3) or partial (13) response to therapy. The 21 day regimen has been combined with cisplatin in 22 patients with extensive stage disease with acceptable results (28).

The starting dose of 40 mg/m^2 for a total of 10 days (Total 400 mg/m^2 in 4 weeks or 100 mg/m^2 per week) was selected because of the study previously performed at the NCI-Navy MOB (6). The dose of etoposide in each cycle used during the first 12 weeks of therapy was 80 mg/m^2 one days 1,2 and 3 of a 3 weeks cycle for a total of 240 mg/m^2 in 3 weeks or 80 mg/m^2 per week. The toxicity of the combined modality regimen using this dose of etoposide during the first 4 cycles of therapy was 15/50 patients (30%) developed grade 4 leukopenia and 5/50 developed febrile neutropenia. In addition 9 of 50 (18%) required hospitalization for dehydration caused by combined modality esophagitis. Previous experience at M.D. Anderson with a 21 day regimen of etoposide at a dose of 50 mg/^{2} per day in conjunction with chest radiotherapy for both non-small cell lung cancer and small cell lung cancer has produced excessive hematologic and esophageal toxicity (B. Glisson and J.S. Lee, personal communication). Therefore, we propose to start with a 12 day course of etoposide at a similar dose rate intensity (100 mg/m^2 per week) combined with the previous dose of chest radiotherapy used at the NCI-Navy Medical Oncology Branch (45 Gy) and increase both the duration and dose of the etoposide as tolerated. The ability to combine a 12-21 day course of etoposide with concurrent chest radiotherapy will allow us to use an active chemotherapeutic agent with increasing doses of chest radiotherapy for patients with limited stage small cell lung.

3.4 Rationale for Cisplatin

Cisplatin is commonly used in the treatment of SCLC. The single agent response rates of cisplatin in patients with small cell lung cancer is approximately 20%. There is no evidence that higher doses of drugs improve response rates or survival over standard doses (29,30). Therefore we propose to use cisplatin in this combination at similar doses to those

used in current phase III studies of SCLC a dose of 80 mg/m^2.

3.5 Rationale for Increasing Doses of Chest Radiotherapy

The response rate of small cell lung cancer to chest radiotherapy alone is approximately 75% (31-33). Chest irradiation can effectively control the cancer which presents in the chest and has cured approximately 3% of selected patients with limited stage disease when used as a single modality (34). Although the addition of chest radiotherapy to combination chemotherapy for patients with small cell lung cancer increases survival in most studies, control of the intrathoracic tumor remains a problem with nearly half of all patients relapsing in the chest (6,15,18). The experience at the NCI-Navy Medical Oncology Branch on the most recent study has been that 30-40% of patients do not have their tumor controlled in their chest (6,18). Retrospective data has shown that increasing doses of chest radiotherapy from 30 Gy to 50 Gy improves local control from 16% to 63% (35). Therefore, we would like to start the chest radiotherapy at our current dosage of 45 Gy in 3 weeks and increase the dose initially by 6 Gy followed by 3 Gy increments to determine the maximum dose of chest radiotherapy which can be given in combination with our chemotherapy.

3.6 Rationale for Alternating Chemotherapy

Alternating combinations of chemotherapy for small cell lung cancer have been studied for more than 10 years. A National Cancer Institute of Canada study which randomized 321 patients with extensive stage small cell lung cancer showed cyclophosphamide, doxorubicin, and vincristine (CAV) alternating with etoposide cisplatin (EP) was superior to CAV alone (36). However, this study could not rule out the possibility that EP was superior to CAV. Two subsequent studies of patients with small cell lung cancer from Japan and the United States which enrolled at total of 777 patients compared CAV, EP, and alternating EP with CAV (37,38). Both studies showed no difference in survival between the three arms in patients with extensive stage small cell lung cancer. In contrast, the survival of patients with limited stage small cell lung cancer treated with the alternating regimen (median, 16.8 months) was longer than patients treated with EP (median 11.7 months) or CAV (median 12.4 months) with a p value of 0.023 and 0.014 respectively. This data suggests that alternating therapy with chest radiotherapy may be better than using a single regimen and current effective combined modality regimens employ alternating combinations. Although there is more data on the use of EP alternating with CAV, in vitro drug sensitivity testing of small cell lung cancer cells at the NCI-Navy Medical Oncology Branch has provided additional data on combinations. We propose to use cyclophosphamide,

doxorubicin, and etoposide (CAVP-16) as the alternating regimen. In the current small cell lung cancer protocols, 124 specimens from 126 patients were sent to the laboratory prior to treatment. Of these 124, 91 contained tumor. Forty cell lines (44%) were established from the 91 tumor-containing specimens by twelve weeks, and of these 38 had *in vitro* drug testing performed against seven chemotherapeutic agents and thirteen combinations of agents that were considered active against SCLC at the time of design of the current trials. Twenty-eight eventually received their *in vitro* best regimen (IVBR) as their second chemotherapy regimen after cisplatin and etoposide in vitro drug sensitivity testing at the NCI-Navy Medical Oncology Branch protocols for small cell lung cancer. The most commonly selected regimen (9 of 28 times) was cyclophosphamide, cisplatin and etoposide but 2 of the 3 drugs are also used in the etoposide cisplatin combination so we have chosen to use the second most commonly selected combination (7 of 28 times) of cyclophosphamide, doxorubicin, and etoposide. Therefore, we will employ 2 cycles of etoposide cisplatin to be able to use this combination during the time of combined modality therapy and then alternate CAVP-16 with EP.

3.7 Rationale for Pretreatment Biopsies

The current study for patients with limited stage small cell lung cancer includes an option for performing a biopsy on patients with limited stage small cell lung cancer for in vitro drug sensitivity testing. Eighteen of the first 50 patients had a biopsy procedure prior to starting therapy. This included mediastinoscopy in 15, a supraclavicular lymph node biopsy in 2, and a lobectomy in 1. Tumor was present in 16 of the 18 tumor specimens. Patients began chemotherapy a median of 4 days after the procedure with a range of 1-15 days. There were no post-op complications. Therefore, carefully selected patients with small cell lung cancer can be safely biopsied prior to the initiation of treatment without causing a significant delay in starting therapy.

The highest frequency of p53 mutations in human cancer are found in tumors and tumor cell lines from patients with small cell lung cancer (12-14). Recent advances in immunology have shown that BALB/c mice can develop p53 specific CD8+ cytotoxic T cells after incubation of spleen cells with a 21 amino acid peptide which contains a portion of the mutated p53 gene product. These cytotoxic T lymphocytes killed BALB/c fibroblasts transfected with the mutant p53 gene which expressed the mutant protein but not fibroblasts transfected with a different mutated p53 gene (39).

The NCI-Navy Medical Oncology Branch has developed the ability to safely biopsy patients with limited stage small cell lung

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cancer and detect p53 gene mutations in tumors, tumor cell lines, and paraffin embedded tissue. We propose to ask patients to undergo a biopsy to obtain tumor tissue for their p53 gene sequence. Patients will be offered the opportunity to participate in a previously approved protocol (MB-272) studying the vaccination of patients with mutated p53 and ras genes. Briefly, lymphocytes are obtained from patients with relapsed cancer, peptide corresponding to the patients mutated p53 or ras sequence, and the lymphocytes are reinfused into the patient. An attempt to grow a tumor cell line from their tumor will also be done to provide target cancer cells to assess immunologic response in the patients following immunization with the specific mutation in their p53 gene.

4 OBJECTIVES

4.1 To determine the maximum tolerated dose of cisplatin and a 12-21 day course of oral etoposide with 45 Gy of BID concurrent chest radiotherapy.

4.2 To determine the maximum tolerated dose of chest radiotherapy administered with the maximum tolerated dose of etoposide cisplatin for patients with limited stage small cell lung cancer

4.3 To determine the spectrum of toxicities for the combination chest radiotherapy administered with concurrent etoposide cisplatin for patients with limited stage small cell lung cancer

4.4 To determine the local control rate of the small cell lung cancer in the chest following treatment with combined modality therapy

4.5 To determine the overall and complete response rates and survival of patients with limited-stage SCLC for the combination chest radiotherapy administered with concurrent etoposide cisplatin for patients with limited stage small cell lung cancer.

4.6 To determine, in a consecutive series of patients with limited-stage small cell lung cancer, the frequency with which adequate cancer tissue for p53 gene sequence can be safely obtained.

4.7 To prepare patient-specific mutant p53 peptide for eventual immunization

5 ELIGIBILITY CRITERIA

5.1 Histologically confirmed diagnosis of SCLC. Mixed small cell/non-small cell carcinoma with predominant small cell

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component will be considered small cell lung cancer. Patients with extrapulmonary small cell lung cancer whose clinically evident tumor can be encompassed within a tolerable radiotherapy portal may be treated on this protocol but will be reported separately from the other patients with limited stage small cell lung cancer.

5.2 No previous chemotherapy or thoracic/cranial radiotherapy.

5.3 Patients with small cell lung cancer must have limited-stage disease defined as disease within the confines of one hemithorax, and bilateral hilar, mediastinal, and supraclavicular nodes. In addition since locally extensive tumor is likely to increase toxicities from irradiation, chest wall involvement, significant pleural effusion (regardless of cytology results), pathologic pleural involvement, pericardial tumor, and massive ipsilateral pulmonary tumor, will be considered extensive-stage disease. Bilateral endobronchial disease (found on bronchoscopy) will be considered limited-stage disease if no other evidence of metastatic disease is discovered. The detectable disease must be encompassable in a tolerable radiation therapy portal.

5.4 No active second malignancy in the past 5 years (excluding squamous or basal cell carcinoma of the skin or carcinoma-in-situ of the cervix).

5.5 Patients must be ambulatory more than half of the day (ECOG performance status of 0-2; Appendix 3).

5.6 Patients must have adequate hematologic, renal and hepatic function, as defined by absolute granulocyte count over $1200/mm^3$, platelet count over $100,000/mm^3$, serum creatinine below 2.0 mg/dl, and bilirubin less than 1.5.

5.7 Major active infections not due to an obstructed bronchus must be controlled.

5.8 No symptomatic heart disease including less than fully compensated congestive cardiac failure, significant arrhythmias, or myocardial infarction within three months.

5.9 No active major psychiatric problems.

5.10 Patients must sign an informed consent and be willing to and have reasonable expectation of return for follow-up.

5.11 Lack of measurable disease (e.g. surgically resected primary tumor) shall not preclude protocol entry in otherwise eligible patients. Patients shall be treated and followed for survival, but not included in response rate calculations.

5.12 Patients must be willing to receive transfusions of blood products if required.

5.13 Female patients must not be pregnant or breast feeding.

6 STAGING PROCEDURES

Pre-treatment staging procedures and study parameters

6.1 Radiation Oncology Consult.

6.2 Complete history and physical examination.

6.3 Chest radiography, PA and lateral.

6.4 Fiberoptic bronchoscopy, with washings & brushings for cytologic examination and biopsies of suspicious lesions. Bronchoscopy will be repeated if the procedure has already been carried out at an outside institution.

6.5 Thoracic CT scan.

6.6 Dedicated hepatic CT scan.

6.7 Bilateral posterior iliac crest bone marrow examinations, with aspirates, touch preps, and biopsies; aspirates sent to cell biology laboratory.

6.8 Paracentesis of pleural, ascitic, or pericardial effusions if present, with fluid sent to the cell biology laboratory.

6.9 Cranial CT scan or MRI scan of brain

6.10 Radionuclide bone scan with bone radiographs of areas that are abnormal or suspicious for metastatic cancer on radionuclide bone scan.

6.11 Liver biopsies will only be performed for diagnostic purposes if the liver is the only potential site of metastatic disease, the dedicated hepatic CT scan is normal or equivocal, and two or more liver function tests (AST, ALP, LDH, & bilirubin) are abnormal (elevated more than 2 fold above the upper limit of normal). A portion of the biopsy specimens should be sent to the cell biology laboratory. If the dedicated liver CT scan is considered positive for metastatic disease, the patient will be scored as having liver metastases and excluded from the trial, irrespective of the number of abnormal LFTs.

6.12 Electrocardiogram

6.13 Complete blood count, including WBC differential and platelet

counts; prothrombin and partial thromboplastin times; serum electrolytes & magnesium, urea & creatinine, glucose, calcium, phosphate, and uric acid; liver function tests, including albumin and total protein; urinalysis.

6.14 Serum and leukocyte storage at the NCI-Navy Medical Oncology Branch

6.15 Lumbar puncture for CSF protein, glucose, cell count, cytology, and culture only if neurologic signs or symptoms warrant.

6.16 Magnetic resonance imaging of the spine only if neurologic symptoms or signs warrant.

6.17 Pulmonary function tests with arterial blood gases

6.18 In order to expedite the staging process, bone marrow examination, paracenteses, and biopsies of accessible nodes or soft tissue lesions should be the first staging procedures performed. If these procedures appear unlikely to yield tumor tissue, Dr. Zech or Hosannah should be notified of a potential candidate for a surgical biopsy.

6.19 Mediastinal Exploration (mediastinoscopy, mediastinotomy or other necessary thoracic surgical procedure shall be performed by Dr. Zech or Hosannah with transport of tumor biopsy material to the cell biology laboratory for attempted cell culture and p53 gene sequencing, in patients in whom the staging procedures listed have not yielded suitable positive tumor specimens for cell culture. If mediastinal or other surgical biopsy is to be performed, there must be no immediate need for chemotherapy and agree to the procedure with full knowledge of its experimental nature, and the patient must be considered a good candidate for general anesthesia by the Senior Staff physicians of the NCI-NMOB, the Thoracic Surgery Department, and the Anesthesiology Department. Patients with superior vena cava syndrome and lobar collapse cuased by the small cell lung cancer will not be considered for these elective surgical procedures. During surgery, the surgeon may elect to resect stage I or II tumors. No attempt will be made to resect tumor in patients with mediastinal involvement with small cell lung cancer.

7 PATIENT REGISTRATION GUIDELINES

7.1 An eligible patients should be registered on this protocol after consultation with the principal investigator, co-investigators, and/or the responsible research nurse. The clinical associate should call the personnel at Orkand at

their central office at 301-402-1732 between the hours of 8:30 A.M. to 5:00 P.M, Monday through Friday. Registrations done during non-duty times are to be called to the Orkand office at the earliest available time after the patient has entered on a study.

7.2 The eligibility requirements outlined in section 5 must be met at the time of registration. Protocol specific eligibility checklists will be developed by the Orkand staff, data manager, and reviewed by the Principal Investigator or Protocol Chairperson.

7.3 A protocol specific consent form must be signed by the patient or guardian and retained in the patient's medical record. A copy of the consent form is in appendix 4.

7.4 After the pretreatment studies are completed and the eligibility has been established, the patient's treatment may begin

7.5 Orkand personnel are to be called at 301-402-1732 at the time patients are taken off the protocol study. The date and reason the patients went off the protocol should be recorded.

8 PHARMACEUTICAL INFORMATION

8.1 Etoposide (VP-16) - VePesid[R], Bristol Myers Squibb, Evansville, Indiana.

8.11 Mechanism of action: Semisynthetic derivative of podophyllotoxin, a cytotoxic drug isolated from the root of the May apple plant. It causes DNA strand breaks by interacting with topoisomerase II.

8.12 Clinical toxicity: The major toxic effects of etoposide are dose-related myelosuppression, nausea and vomiting, and alopecia. Transient hypotension following rapid intravenous administration has been reported in 1-2% patients. Less frequent toxicities include diarrhoea, stomatitis, peripheral neurotoxicity, and allergic reactions. The long-term administration of etoposide has been associated with development of leukemia.

8.13 Clinical formulation: Etoposide is commercially available and will be supplied by CTEP, DCT, NCI. Oral etoposide is available as 50 mg capsules which bear an expiration date and should be stored at 2-8°C. VePesid injection is supplied as 100 mg/5mL sterile multiple dose vials. The injection must be diluted prior to use with either 5% Dextrose or 0.9% Sodium

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Chloride solution to give a final concentration of 0.2-0.4 mg/mL. It should not be given by rapid intravenous injection.

8.2 Cisplatin - Platinol[R], Bristol Myers Squibb, Evansville, Indiana.

8.21 Cisplatin has biochemical properties similar to that of bifunctional alklating agents, producing interstrand and intrastrand cross-links in DNA. It is cell-cycle non-specific.

8.22 Clinical toxicity: Dose-related and cumulative renal insufficiency is the major dose-limiting toxicity. Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Other common toxicities include marked nausea and vomiting, hypomagnesemia and other electrolyte disturbances, ototoxicity, peripheral neurotoxicity, and moderate myelosuppression, anemia, and thrombocytopenia. Less commonly vascular toxicities such as thrombotic microangiopathy, cerebral vasculitis and cerebrovascular accident have been described. Hyperuricemia, optic neuritis, allergic reactions, L'hermitte's sign and autonomic neuropathy have all been reported in association with the administration of Cisplatin.

8.23 Clinical formulation: Cisplatin is commercially available as powder in 10 mg and 50 mg vials containing mannitol and sodium chloride <u>and will be supplied by CTEP, DCT, NCI</u>. Intact vials bear an expiration date and should be stored at room temperature. When 10 mL or 50 mL of sterile water is added to the respective vials, the drug is at a concentration of 1 mg/mL in normal saline. The drug is diluted further in normal saline to a concentration of 0.05 or 0.5 mg/mL and infused into a running IV line over 1 hour.

8.3 Doxorubicin Hydrochloride - Adriamycin[R], Adria, Columbus, Ohio.

8.31 Mechanism of action: Doxorubicin is a cytotoxic anthracycline antibiotic isolated from cultures of *Streptomyces peucetius*. Complex mechanisms underlie anthracycline cytotoxicity. Firstly adriamycin binds to nucleic acids, presumably by specific intercalation of the planar anthracycline nucleus with the DNA double helix and disrupts DNA replication and transcription. Second, it can produce single- and double-stranded DNA scission and impair DNA repair. The process of DNA scission may be facilitated by intercalation between base pairs or by an intercalation with topoisomerase II. A third mechanism of generating DNA breaks and many other forms of damage is the creation of free radicals. Finally doxorubicin may also kill cells by disruption of the cell membrane.

8.32 Toxicity: Dose-limiting toxicities are myelosuppression and cardiotoxicity. Serious irreversible myocardial toxicity with delayed congestive failure often unresponsive to any cardiac supportive therapy may be encountered as total dose of the drug approaches 550 mg/m^2. This toxicity may occur at lower cumulative doses in patients with prior mediastinal irradiation or on concurrent cyclophosphamide therapy. Other common toxicities include reversible alopecia and acute nausea and vomiting. Phlebosclerosis does occur, particularly when small veins are used for administration. Severe cellulitis, vesication and tissue necrosis occur if the drug is extravasated during administration. Allergic reactions, conjunctivitis and lacrimation have been rarely reported.

8.33 Clinical formulation: Adriamycin is commercially available as a lyophilized powder in 10 mg, 20 mg, and 50 mg single use vials and 150 mg multi-dose vials and will be supplied by CTEP, DCT, NCI. It should be reconstituted with 5 mL, 10 mL, 25 mL, and 75 mL respectively, of 0.9% sodium chloride solution to give a final concentration of 2 mg/mL. The reconstituted solution is stable for 7 days at room temperature and under normal room light and 15 days under refrigeration. It should be protected from exposure to sunlight. It should be administered into a free-running infusion of 0.9% sodium chloride.

8.4 Cyclophosphamide - Cytoxan^R, Bristol Myers Squibb, Evansville, Indiana.

8.41 Mechanism of action: Cyclophosphamide is an alkylating agent and therefore non-cell cycle specific. It is an inert compound that is metabolized to liberate the active phosphoramide mustard. This compound forms positively charged carbonium ions that form covalent bonds with electron-rich groups in nucleic acids, proteins, and an array of smaller molecules. DNA alkylation produces a variety of defects including depurination, double- and single-stranded breaks, inter- and intrastrand cross-links, which disrupt DNA replication and transcription.

8.42 Toxicity: The most common toxicities include reversible myelosuppression, acute nausea and vomiting, and alopecia. Sterile hemorrhagic cystitis can occur, and usually resolves spontaneously within a few days of interrupting cyclophosphamide therapy. If it becomes a significant problem, the uroprotectant Mesna can be used as prophylaxis. Gonadal suppression, resulting in amenorrhea or azospermia, has been reported and appears related to dosage and duration of therapy. Higher doses of cyclophosphamide can cause mucositis, pulmonary fibrosis, syndrome of inappropriate antidiuretic hormone secretion, and cardiac toxicity manifested by heart failure. Second malignancies have been reported in patients

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treated with cyclophosphamide alone and in combination with other chemotherapeutic agents.

8.43 Clinical formulation: Cytoxan is commercially available as a sterile powder containing 45 mg sodium chloride per 100 mg anhydrous cyclophosphamide and will be supplied by CTEP, DCT, NCI. It is available in 100 mg, 200 mg, 500 mg, and 1000 mg vials. It should be stored at temperatures not exceeding 25°C and should be reconstituted with sterile water. The reconstituted solution must be used within 24 hours if stored at room temperature or within 6 days if stored at 2-8°C.

8.5 Vincristine sulphate - Oncovin, Bristol Myers Squibb, Evansville, Indiana.

8.51 Mechanism of action: Vincristine binds to tubulin, a dimeric protein that normally polymerizes to form the microtubular apparatus along which chromosomes migrate during mitosis. Binding of vincristine to tubulin prevents the proteins polymerization, causing the cells to be arrested in metaphase and subsequently lysed.

8.52 Toxicity: Dose-limiting toxicity is neurotoxicity, manifested by peripheral neuritis, gastrointestinal neuropathy (constipation to paralytic ileus) and cranial nerve palsies. Myelosuppression is usually insignificant and there is little effect on platelet and red blood cell levels. Rare complications include syndrome of inappropriate antidiuretic hormone secretion, allergic reactions, severe bronchospasm especially when used in combination with mitomycin-C, and alopecia. Extravasation of the drug into the surrounding tissues causes irritation, cellulitis, vesication and occasionally ulceration. It should be treated immediately with local injection of hyaluronidase and application of moderate heat to attempt to disperse the drug.

8.53 Clinical formulation: Vincristine is commercially available as a 1 mg/mL solution in 1 mL, 2 mL, and 5 mL vials and will be supplied by CTEP, DCT, NCI. It should be stored in the refrigerator at 2-8°C. The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion.

9 TREATMENT PROGRAM

9.1 Etoposide Cisplatin (EP) Regimen

9.11 Etoposide is given as an oral course for cycles 1, 2, 4, and 6. The starting dose of etoposide will be 40 mg/m^2/day on days 1-5 and 8-12 day on a 28 day cycles. After the first cycle of etoposide therapy when the chest irradiation is

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completed, the etoposide will be administered on consecutive days in cycles 2, 4, and 6. Cisplatin will be administered on day 1 at 80 mg/m^2.

9.2 Thoracic Radiation

9.21 The Radiation Oncology Branch and Senior Staff Oncologists will agree on the patient's eligibility before the thoracic surgical procedure. Simulation will take place prior to other therapy.

9.22 A greater extend of tumor spread identified on during the thoracic procedure shall not exclude patients from combined modality therapy. In addition, if the biopsy specimen taken during the elective thoracic surgical procedure for obtaining tumor tissue for experimental purposes has lung cancer histologies other than small cell lung cancer, the patient will still be treated on this protocol.

9.23 The thoracic megavoltage therapy will be started on the same day as the first course of EP following appropriate simulation.

9.24 Patients will be treated isocentrically on a megavoltage radiotherapy unit (4-15meV X-rays). Usually opposing field treatment will be employed as most small cell neoplasms of the lung are midplane. Should an individual's neoplasm be eccentrically placed, more sophisticated treatment planning will be allowed. All fields will be irradiated each day of treatment.

9.25 Most patients will be treated supine on a couch. For those patients whose tumor flattens laterally in the prone position, resulting in an inappropriate inclusion of additional normal lung within the treatment volume, therapy will be given in the ROB isocentric chair at the NCI.

9.26 All patients will be simulated and undergo computerized treatment planning prior to the start of treatment. Patients will be reevaluated for tumor shrinkage on a weekly basis. If significant reduction in tumor volume has occurred the patient maybe resimulated using a reduced field with adequate tumor margin (1-2 cm) in an attempt to reduce normal tissue toxicity.

9.27 Initially the original tumor volume will be included with a 1-2 cm margin. Involved mediastinal nodes will be included along with the ipsilateral hilum. The contralateral hilum, uninvolved mediastinum and uninvolved supraclavicular regions will not necessarily be included."

9.28 Fractionation for the chest neoplasm will start at 150 cGy

b.i.d to a total dose of 4500 cGy/30 fractions/3 weeks. B.i.d fractions will routinely be delivered at least 6 hours apart (minimum of 4 hours apart). In the event b.i.d treatment can not be given, a single 250 cGy fraction will be delivered. The single 250 cGy fraction will not be used routinely but may be used on holidays, weekends, or in the event of an emergency in the Radiation Oncology Department.

9.29 Computer generated CT treatment planning will be used in all cases. CT treatment plans will be generated from CT cuts at the isocentric plane, 2 cm below the top of the field, 2 cm above the bottom of the field, and at other areas of interest (such as the area of the heart which may receive the maximum dose) as directed by the staff radiation oncologist. In addition, a lateral simulation x-ray will be taken and a sagittal dose distribution plan will be generated to evaluate maximum spinal cord dose. Tumor dose will be prescribed to either a minimal tumor midplane dose or to an isodose line (generally 95% to 100% line) which completely surrounds the tumor in the isocentric plane. Both a maximum spinal cord dose and maximum heart dose (if heart is in the field) will be recorded in the radiation treatment record.

9.210 The maximal spinal cord dose will be determined from the sagittal spinal cord dose distribution as described in para. 9.29. Orientation of treatment fields and blocking changes will be made as necessary to insure that the total spinal cord maximum point dose does not exceed 4500 cGy. A posterior spinal cord block may be used only in unusual situations such as bilateral supraclavicular involvement where full radiation therapy doses can not delivered using standard techniques (APPA, obliques) without exceeding a spinal cord tolerance.

9.3 **Cyclophosphamide, Doxorubicin, Etoposide (CAVP-16) Regimen**

9.31 Cyclophosphamide will be at a dosage of 1000 mg/m^2, on day 1, doxorubicin at a dosage of 45 mg/m^2 on day 1, and etoposide at a dosage of 80 mg/m^2 on days 1, 2 and 3 of cycles 3, 5, and 7.

9.4 TREATMENT SCHEDULE

Cycle 1	Cycle 2	Cycles 3,5,7	Cycles 4,6
Weeks 1-3	Weeks 4-6	Weeks 8,15,21	Weeks 11,18
ET D 1-12/19 CP D 1	ET D 1-12/19 CP D 1	CTX D 1 ADR D 1 ET D 1,2,3	ET D 1-12/19 CP D 1
Chest RT	-	-	-

9.41 The treatment cycles will be repeated every 21-28 days if blood counts permit and non-hematologic toxicity has resolved

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9.42 Patients will be either hospitalized or remain in the Washington, DC area for their course of combined modality therapy (weeks 1-3) to be observed for potential toxicity.

9.43 A total of 7 cycles of chemotherapy will be administered

9.44 Prior to the 5th cycle of chemotherapy patients will undergo limited restaging, with evaluation of previously identified sites of tumor involvement. All patients without evidence of tumor progression will continue combination chemotherapy administration

9.45 After 7 cycles of therapy, all patients will undergo restaging procedures to determine response to therapy. Chemotherapy will be discontinued in all patients not demonstrating tumor progression. Patients who develop progressive disease at any time will have efforts made to obtain further tumor biopsies for in vitro testing drug testing and attempts at establishing tumor cell lines.

9.46 Patients with small cell lung cancer deemed to be in complete remission will be offered elective cranial irradiation. Patients whose cancer has resolved by chest radiograph and have a partial remission because of evidence of residual disease within the radiation portal detected only by CT scan will also be offered elective cranial irradiation.

9.5 Etoposide Administration

Etoposide will be given at an initial dose of 40 mg/m^2/day on days 1-5 and 8-12 if the patients start their chest irradiation on Monday (Patients should not initially take etoposide on weekend days when they are not receiving chest irradiation). If the chest irradiation starts on a day other than Monday, the etoposide should start on the day chest irradiation commences and etoposide not should be taken during the weekend when chest radiation is not administered.

Etoposide is commercially available in 50 mg capsules. The dose per week should be determined by computing the number of square meters of the patient, multiplying by 50 (the dose per square meter of etoposide), and then the number of days per week. This is divided by 50 mg to arrive at the number of capsules per week and this number of capsules is given in divided doses over 5 to 7 days as outlined in the following table:

BSA	Cum 5 D Dose @ 40 mg/m^2	BSA	Cum 5 D Dose @ 50 mg/m^2	BSA	Cum 7 D Dose @ 50 mg/m^2
1.2-1.4	5	1.2-1.3	6	1.2	8

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1.5-1.6	6	1.4-1.5	7	1.3	9
1.7-1.8	7	1.5-1.6	8	1.4-1.5	10
1.9-2.1	8	1.7-1.8	9	1.6	11
2.2-2.4	9	1.9-2.0	10	1.7	12
		2.1-2.2	11	1.8-1.9	13
		2.3-2.4	12	2.0	14
				2.1-2.2	15
				2.3	16
				2.4	17

Following completion of chest radiotherapy (cycles 2, 4, and 6) the etoposide should be administered on consecutive days (level 1 on days 1-10, level 2 and 3 on days 1-15).

The patients will be seen 5 times weekly and should have their complete blood count checked two times per week during their initial 4 weeks of therapy. Dose modifications will be as outlined in section 10.0

Patients treated as outpatients should be seen weekly in the hematology oncology clinic during their concurrent therapy.

9.6 Cisplatin Administration

9.61 The hydration prior to administration of intravenous cisplatin shall consist of D5W plus 0.5 Normal Saline with 20 milliequivalents of KCL/liter administered at 350 milliliters per hour for a total of 2 liters. At the completion of the first liter of fluid, 20 mg of furosemide is administered and the dose of cisplatin is administered in solution with 12.5 grams of mannitol in conjunction with the second liter of fluid. Additional intravenous furosemide may be used if the urine output is not maintained at an adequate level (greater than 100 mls/hours).

9.62 Cisplatin 80 mg/m^2 will be given on day 1 as a 30 minute intravenous infusion between their morning and afternoon dose of chest radiation. Dose modification of cisplatin will be as described in section 10.

9.7 Dose escalation scheme for etoposide administration

Level	Etoposide Schedule	Tot Dose

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Level 1	40 mg/m^2 PO Days 1-5 and 8-12	400 mg/m^2
Level 2	40 mg/m^2 PO Days 1-5, 8-12, 15-19	600 mg/m^2
Level 3	50 mg/m^2 PO Days 1-5, 8-12, 15-19	750 mg/m^2
Level 4	50 mg/m^2 PO Days 1-21	1050 mg/m^2

9.71 At least 3 new patients will be entered at each dose level. At least 3 patients treated at a given dose level must be fully evaluable for 3 months from the start of chemotherapy before entry of additional patients at a higher dose level.

9.72 If no dose limiting toxicity as defined in section 9.41-9.46 is seen at a given dose level, then 3 new patients will be entered at the next higher etoposide dose level.

9.73 If 1 patient entered at a given dose level experiences dose-limiting toxicity as defined in section 9.9, 3 additional patients may be entered. If 2 patients entered at a given dose level experience dose-limiting toxicity as defined in section 9.9, then no additional patients will be entered at that dose level. At least 3 additional patients will be entered at one dose level below to more precisely define toxicity patterns at the lower dose level.

9.74 Dose escalation of etoposide will cease if two or more patients experience dose-limiting toxicity at a given dose level as defined in section 9.9

9.75 The recommended phase II dose for this regimen will be one level below that dose level which produces dose-limiting toxicity (defined in section 9.9) in one-third or more of the patients treated at a given dose level.

9.76 The recommended dose of etoposide in this combination of etoposide cisplatin with concurrent chest radiation be at the level outlined in 9.75. The dose of etoposide will be fixed at the maximum tolerated dose and the dose escalation of chest radiotherapy will commence.

9.8 Dose escalation scheme chest radiotherapy

Level	Schedule of Chest RT	Dose
Level 1	1.5 Gy BID 5 Days per Week X 15 Days	45 Gy
Level 2	1.5 Gy BID 5 Days per Week X 17 Days	51 Gy
Level 3	1.5 Gy BID 5 Days per Week X 18 Days	54 Gy
Level 4	1.5 Gy BID 5 Days per Week X 19 Days	57 Gy
Level 5	1.5 Gy BID 5 Days per Week X 20 Days	60 Gy

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9.81 At least 6 new patients will be entered at each dose level. All six patients treated at a given dose levels must be fully evaluable for 3 months from the start of chemotherapy before entry of additional patients at a higher dose level.

9.82 If 0 or 1 patient experience dose limiting toxicity as defined in section 9.9 at a given dose level, then 6 new patients will be entered at the next higher chest radiation dose level.

9.83 If 2 patients entered at a given dose level experiences dose-limiting toxicity as defined in section 9.9, then no additional patients will be entered at that dose level. At least 6 additional patients may be entered at one dose level below to more precisely define toxicity patterns at the lower dose level.

9.84 Dose escalation of chest radiation will cease if two or more patients at a given dose level experience dose-limiting toxicity as defined in section 9.9.

9.85 The recommended dose of chest irradiation for this regimen will be one level below that dose level which produces dose-limiting toxicity (defined in section 9.9) in one-third or more of the patients treated at a given dose level.

9.86 The recommended chest radiation dose with this combination of etoposide cisplatin alternating with cyclophosphamide, doxorubicin, and etoposide will be at the level outlined in 9.85

9.87 An additional 6 patients may be entered at the recommended chest radiation dose to document that the regimens are truly tolerable

9.9 Dose Limiting Toxicities*

9.91 White blood cell (WBC) dose-limiting toxicity is defined during the first 2 cycles days (56 days) of therapy by:

1. Asymptomatic grade 4 leukopenia or neutropenia (WBC <1000/microliter, or absolute granulocyte count (AGC) <500/microliter lasting ≥ 7 days

2. Occurrence of more than 1 episode of febrile neutropenia or a single episode which requires intravenous antibiotics for more than 5 days

3. Occurrence of neutropenic sepsis

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9.92 Platelet dose-limiting toxicity during the first 2 cycles (56 days) of therapy by:

1. A platelet count of ≤ 25,000/microliter lasting more than 7 days

9.93 Combined modality pneumonitis dose-limiting toxicity during the course of therapy is defined by:

1. Fatal pneumonitis characterized by shortness of breath and bilateral pulmonary infiltrates which extend beyond the radiation portals which is not caused by infectious etiologies.

2. Grade 4 acute or chronic pulmonary toxicity

*Defined by the EORTC/RTOG Acute and Chronic Radiation Morbidity Scoring Criteria

9.94 Combined modality esophagitis dose-limiting toxicity during the course of therapy is defined by:

1. Grade 3 acute combined modality esophagitis requiring more than 7 days of nasograstric feedings or intravenous hydration or grade 4 acute combined modality esophagitis.

2. Grade 3 chronic combined modality esophagitis requiring more than 10 esophageal dilations, chronic narcotics for analgesia, or grade 4 chronic combined modality esophagitis

*Defined by the EORTC/RTOG Acute and Chronic Radiation Morbidity Scoring Criteria

9.95 Other dose-limiting toxicity is defined by:

1. Any grade 4 toxicity

2. Any grade ≥ 2 toxicity which fails to resolve by day 36.

9.10 Duration of Treatment

Patients will be treated for a total of 7 cycles of chemotherapy if the patient is tolerating the therapy unless there is obvious tumor progression. Patients who progress while on therapy will have the option of no further therapy or available phase I, phase II, or other conventional agents.

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10 DOSE MODIFICATION FOR ETOPOSIDE CISPLATIN ADMINISTRATION

10.1 The second cycle of etoposide cisplatin should begin on the schedule date (day 29) despite hematologic toxicity as outlined in section 9. If other grade 3 or 4 toxicity is encountered that is dose limiting, the dose of etoposide for the second cycle should be decreased by 1 level.

10.2 In cycles 4 and 6, the etoposide cisplatin should begin on schedule (day 22) if the following criteria are met.

1. The WBC is ≥ 4000/microliter and the AGC is ≥ 2000.

2. The platelet count is ≥ 100,000/microliter

3. Any non-hematologic toxicity is ≤ grade 1 other than acute esophageal toxicity which may be up to grade 2 and up to grade 3 acute pulmonary toxicity.

A one week delay is permitted to allow for the recovery of hematologic and non-hematologic toxicity for cycles 3-7. If after 1 week the toxicity has not resolved, dose adjustments as outlined in section 10 should be followed.

10.3 Dose Modification for oral and intravenous etoposide **for cycles 4 and 6**. The dose of oral etoposide should decreased by 1 level for any of the following:

1. Asymptomatic grade 4 leukopenia or neutropenia (WBC <1000/microliter, or AGC < 500/microliter) lasting greater than 7 days, or

2. Occurrence of febrile neutropenia, or

3. Occurrence of neutropenic sepsis

4. A platelet nadir of ≤ 25,000/microliter

10.4 Dosage modification for cisplatin

10.41 If the serum creatinine is increased by less than 2-fold since the start of the previous cycle and is 2.5mg/dL or less, administer the dose as outlined in section 9.22

10.42 If the serum creatinine is more than doubled since the start of the previous cycle and between 2.0 & 2.5mg/dl or is 2.5-4.0 mg/dL and the patient is receiving 80 mg/m^2 of cisplatin, the patient should have the dose decreased to 60 mg/m. If the patient is receiving 60 mg/m^2 of cisplatin and experiences this degree of renal toxicity, the cisplatin should be discontinued and the patient

treated with etoposide alone.

10.43 If the renal toxicity is greater than outlined above, the cisplatin should be discontinued and the patient treated etoposide alone.

10.44 If dose modifications are necessary for patients on level I of the dose escalation scheme for etoposide cisplatin, because of toxicity, the dose of etoposide should be reduced by the increments to Level -1 (40 mg/m^2 PO days 1-5 and 8-10) and Level -2 (30 mg/^{2} PO days 1-5 and 8-10) If the modifications of the radiation are necessary at the starting dose, the dose should be reduced by increments of 3 Gy (i.e. Level -1: 1.5 Gy BID 5 Days per Week X 14 Days 42 Gy, Level -2: 1.5 Gy BID 5 Days per Week X 13 Days 39 Gy)

11 Cyclophosphamide, Doxorubicin, Etoposide (CAVP-16) Regimen

11.1 Cyclophosphamide Administration

Cyclophosphamide 1000 mg/m^2 will be given on day 1 of cycles 3, 5, and 7 as an intravenous bolus over 15-30 minutes.

11.2 Doxorubicin Administration

Doxorubicin 45 mg/m^2 will be given on day 1 of cycles 3, 5, and 7 slowly as an intravenous push.

11.3 Etoposide Administration

Etoposide 80 mg/m^2 will be given on days 1, 2 and 3 of cycles 3, 5, and 7 over 30-60 minutes in 250 to 500 millilieters of normal saline.

12.1 Hematologic Toxicity

12.11 Myelosuppression can be caused by etoposide (VP-16), cyclophosphamide, doxorubicin

12.12 Each course of therapy can be delayed for up to one week for hematologic recovery, or longer if severe infection, thrombocytopenia-associated bleeding, or other life-threatening toxicity or medical complication is present. Hematologic recovery is defined as AGC over 1000/mm^3 and platelet count over 100,000/mm^3.

12.13 If hematologic recovery has not occurred after a one week delay, then the next course of treatment with intravenous cyclophosphamide, doxorubicin, and intravenous etoposide should be given with the following dosage modifications: Counts on day of Treatment

AGC (/mm^3)	Platelets (x10^3/mm^3)	Dose administered (%)
≥ 1000	≥100	100
750-1000	75-99	75
500-750	50-74	50
<500	<50	0

12.14 The lower dose that is dictated by either the AGC or platelet count is the dose that should be given. If granulocytopenic fever, thrombocytopenia-associated bleeding, or need for platelet transfusions has occurred during the previous course of treatment, a Senior Staff Physician must be consulted regarding possible further dosage reductions. If AGC is < 500/mm^3 or platelets < 50,000/mm^3 for more than two weeks after treatment is scheduled, a bone marrow examination should be performed.

Cyclophosphamide:100% when creatinine < 3.5 mg/dL
50% when creatinine > 3.5 mg/dL

12.3 Hepatic Toxicity

12.31 No drugs used in this trial will commonly cause hepatic toxicity.

12.32 Dosage modification is required for doxorubicin if the serum bilirubin is elevated:

Serum Bilirubin (mg/dL)	Dose (%)
< 2.0	100
2.0-3.0	75
3.1-5.0	50
> 5.0	none

12.4 Hemorrhagic cystitis:

12.41 Hemorrhagic cystitis is not common with cyclophosphamide used at these doses.

12.42 If hemorrhagic cystitis occurs after cyclophosphamide administration, the subsequent dose should be reduced by 50% and IV hydration increased both before and after drug administration. If no cystitis then occurs at reduced dosage, full dose with increased hydration may be tried at the next cycle.

12.43 Severe recurrent cystitis will lead to cessation of the offending drug and substitution with another alkylating

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agent to be determined by the Principal Investigator.

12.5 Mucositis and Enteritis

12.51 Mucositis can be caused by radiation, doxorubicin, and etoposide.

12.52 Dosage modifications for mucositis other than esophageal toxicity should be discussed with the Principal or Associate Investigators.

12.6 Peripheral Neuropathy

12.61 Peripheral neuropathy can be caused by cisplatin, and to a much lesser extent VP-16

12.63 Dosage modifications for neurotoxicity caused by cisplatin or VP-16 should be discussed with the Principal Investigator or Associate Investigators.

12.7 Cardiac Toxicity

12.71 Doxorubicin can cause acute arrhythmias on intravenous administration and congestive cardiac failure, particularly when the cumulative dose administered exceeds 550 mg/m^2.

12.72 All patients will have an EKG performed prior to therapy with doxorubicin and a nuclear gated cardiac scan if medically indicated. Doxorubicin will only be administered if there are no significant cardiac abnormalities. It will be discontinued if cardiac failure or unexplained arrhythmias develop on therapy.

12.8 Decreased Auditory Acuity

12.81 Hearing loss can be caused by cisplatin although it is most often high frequency hearing loss detected on audiogram and not clinically.

12.8.2 If clinically detectable hearing loss occurs then the patient should be referred for an audiogram. If the results show severe impairment, the Principal Investigator or other Senior Staff should be notified prior to administering further cisplatin.

12.9 Acute Nausea and Vomiting

12.9.1 All drugs in this study can cause acute nausea and vomiting.

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12.9.2 Prophylactic anti-emetics will be administered as required, and nausea and vomiting that does occur will be evaluated and treated symptomatically.

12.11 Alopecia

12.11.1 Most drugs used in this study will cause alopecia. Drug dosage will not be altered for this side-effect, but wigs can be provided if the patient desires.

12.13 Because of the usual advanced age of the patients, the frequency of sterility and teratogenicity associated with chemotherapy of SCLC has not been specifically studied. However, the drugs used would be expected to have these side-effects. There may be a small risk of secondary leukemia associated with modern therapy of SCLC, but this risk (currently less than 0.1% and actuarially calculated at 4% at 5-10 years in our experience of all patients) is far outweighed by the survival benefits compared to no treatment.

13 STUDY PARMETERS DURING THERAPY

13.1 Complete blood count will be performed twice weekly and as clinically indicated during the first two cycles of therapy, and then at least prior to each subsequent course of therapy.

13.2 Blood chemistry (serum electrolytes & magnesium, urea & creatinine, glucose, calcium, phosphate, and uric acid; liver function tests, including albumin and total protein) will be performed weekly during the first two cycles of therapy and then at least prior to each subsequent course of therapy.

13.3 Chest radiography, PA and lateral, at the commencement of each cycle of therapy, or more frequently if indicated.

13.4 Limited assessment of disease response after 4 cycles

13.4.1 Chest radiography, PA and lateral.

13.4.2 If the disease is not evaluable by chest radiograph, the patient should have the imaging study which reveals the evaluable disease each 2 cycles.

13.4.3 Routine neurologic history and examination every 2 cycles

13.5 **Assessment of Response at the Completion of Therapy**

13.5.1 Repeat all procedures listed in sections 6.2 to 6.12. Patient who did not have initial involvement of the bone marrow should not have the bone marrow examination

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repeated

13.5.2 Routine neurologic history and examination on a yearly basis of all patients. Cranial CT and MRI scans every two years.

13.6 Reassessment of tumor involvement at the time of tumor progression

13.6.1 At the time of tumor progression, feasible restaging should be performed for patients with SCLC, including if possible chest radiography, fiberoptic bronchoscopy, bone marrow examinations, biopsy of accessible nodes and soft tissue lesions, cranial CT scan if there are neurologic signs and symptoms, dedicated hepatic CT scan if their are abnormal liver function tests, and radionuclide bone scan with plain radiographs of abnormalities on the scan. Potentially positive tumor specimens should be submitted to the cell biology laboratory.

14 PROPHYLACTIC CRANIAL IRRADIATION

14.1 Prophylactic cranial irradiation will be offered to all patients with SCLC who obtain a complete remission. Patients whose cancer has resolved by chest radiograph and have a partial remission because of evidence of residual disease within the radiation portal detected only by CT scan will also be offered elective cranial irradiation.

14.2 Patients will be treated using an opposed lateral technique. The field will include the entire cranial contents with the bottom of the field extending to the bottom of the C-2 vertebral body. All patients will undergo simulation with custom blocking being used to spare normal tissues.

14.3 Fractionation will be 200 cGy/fraction x 15 fractions for a total dose of 3000 cGy dosed to the isocentric midplane.

14.4 Patients who refuse prophylactic cranial irradiation will remain eligible to continue on the protocol.

15 DEFINITIONS

15.1 Limited-stage small cell lung cancer: Small cell lung cancer within the confines of one hemithorax, or including the bilateral hilar, bilateral mediastinal, and bilateral supraclavicular nodes which is emcompassable within a tolerable radiotherapy portal.

15.2 Complete response (CR): No detectable clinical or radiologic

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evidence of cancer, with pathologic documentation of lack of involvement of previously involved sites, when medically possible. A CR must persist for 4 weeks or longer. If all other staging examinations show disappearance of all evidence of tumor, bone radiographs need only be improved or stable, and radionuclide bone scans shall not negate the designation of a CR.

15.3 Partial response (PR): Greater than 50% reduction in the sum of the areas of measurable or evaluable tumor lesions, persisting for at least 4 weeks. If all other restaging examinations show partial disappearance of all evidence of tumor, bone radiographs need only be improved or stable, and radionuclide bone scans shall not negate the designation of a PR.

15.4 No response (NR): Lack of CR or PR.

15.5 Progressive disease (PD): Appearance of new areas of malignant disease, or greater than 25% increase in the area of measurable or 50% increase in the area of evaluable disease.

15.6 Survival: Measured from day 1 of chemotherapy to the last day of follow-up or death.

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16 SUPPORTIVE CARE AND ADDITIONAL TREATMENT

16.1 The best available supportive care will be given to every patient.

16.2 Patients will typically be hospitalized during the initial invasive staging investigations and the initial of treatment with etoposide cisplatin and chest radiotherapy. Further hospitalization is not mandatory except for major staging procedures and when medically indicated.

16.3 Administration of antineoplastic agents not mentioned in the protocol is not permitted. Corticosteroids are permissible for the development of cerebral metastases and spinal cord compression, and appropriate management of other medical problems that arise during the course of therapy.

16.4 The current initial anti-emetic regimen for use with intravenous chemotherapy is ondansetron 0.15 mg/kg intravenously 30 minutes before chemotherapy as well as 4 and 8 hours after chemotherapy. The patients should then receive ondansetron 8 mg PO TID for 3 days and then discontinue the drug. Anti-emetic therapy may be individualized for each patient and advances in antiemetic regimens should be used for the patients.

16.5 Radiotherapy may be given for brain metastases, epidural metastases or impending pathologic bone fractures during therapy if the patients develop metastases in these sites. Intrathecal chemotherapy to appropriate sites of the central nervous system in patients developing carcinomatous leptomeningitis is appropriate.

16.6 Pericardiocentesis with catheter drainage or other surgical procedure will be carried out if indicated after cardiologic consultation for patients with actual or impending cardiac tamponade during therapy.

16.7 Red blood cell transfusions will be administered if the patients develop significant symptoms of anemia. Platelet transfusions should be considered prophylactically for counts below 20,000/mm^3, or for levels above that when medically indicated.

16.8 Appropriate broad spectrum antibiotics will be given for fever in neutropenic patients.

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17.0 RECORD KEEPING AND DATA REPORTING

17.1 All patient information will be collected by the fellow assigned to each patient and the research nurses.

17.2 The principal and medically responsible investigators will assess all information collected and enter it prospectively into the NCI-Navy Medical Oncology Branch Clinical Information System kept on the Data General or its successor computer in the NCI-Navy Medical Oncology Branch.

17.3 All toxicities will be reported according to the RTOG/EORTC Acute and Late Radiation Morbidity Scoring Scheme and Common Toxicity Criteria shown in appendix 4. Adverse drug reactions must be reported to the Investigational Drug Branch (IDB), and the Committee for the Protection of Human Subjects-National Naval Medical Center, and the Institutional Review Board, National Cancer Institute using the common toxicity criteria outlined in appendix 4. The NCI protocol number must be included on all reports. Report by phone to the IDB within 24 hours at (301) 230-2330, available 24 hours with a recording after working hours:
1) All fatal and life-threatening reactions (Grades 4 & 5) which may be due to drug administration.
2) All fatal events.
3) The first occurrence of any toxicity (regardless of grade) not previously seen with any of the drugs.
A written report using the NCI protocol number and CTEP protocol number is to follow within 10 working days to: Investigational Drug Branch, P.O. Box 30012, Bethesda, MD 20814.

17.5 Data prospectively entered will include:
General patient information including, SS#, DOB, age, smoking history, usual occupation, date of diagnosis, and gender.

17.6 Entry date on protocol.

17.7 Pertinent history and examination, including performance status, weight loss, respiratory, neurologic and other relevant symptoms and signs and smoking and exposure history.

17.8 Results of all staging procedures.

17.9 Dates of all treatments, doses give, and reasons for dose modifications or delays.

17.10 Toxicity as per appendix 4.

17.11 Date and response assessment at each restaging.

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17.12 Date and site/sites of first relapse.

17.13 Treatment after relapse, including dates, dose modifications, toxicity, response and final outcome.

17.14 Date of last clinic review (including status) or death.

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18.0 STATISTICAL CONSIDERATIONS

18.1 The primary endpoint for this trial is the determination of the maximum tolerated dose of oral etoposide with cisplatin and chest radiotherapy followed by the maximum tolerated dose of chest radiotherapy with the maximum tolerated dose of oral etoposide and cisplatin. If 3 patients are entered at each the 4 levels of etoposide escalation (12) with an additional 6 patients added at or just below the maximum tolerated dose for the regimen, approximately 18 patients will be needed. If 6 patients are entered at each dose of the 4 levels of increasing doses of chest radiation (24) with an additional 12 patients added at or just below the maximum tolerated dose for the regimen, approximately 36 patients will be needed for the dose escalation of chest irradiation. Allowing for patient drop out or need to enter some additional patients at intermediate doses, a total of 54 patients may need to be accrued. The estimated duration of accrual will be 5 years.

18.2 The response data, survival, and in vitro drug testing will be collected but not analyzed with pre-determined endpoints.