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TREATMENT OF LIMITED SMALL CELL BRONCHOGENIC CARCINOMA CHEMOTHERAPY ALONE OR WITH RADIATION THERAPY

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ENCLOSURE (43)

Small Cell Carcinoma Protocol

A1 Induction

Cytoxan	1500mg/M^2 IV Days 1 and 22
CCNU	100mg/M^2 PO Day 1
Methotrexate	15mg/M^2 PO Day 1,4,8,11 and Day 22,25,29,32

A2 Maintenance

Cytoxan	500 mg/M^2 IV Day 1 and 22
CCNU	50mg/m^2 PO Day 1
MTX	10mg/M^2 PO Day 1,4,8,11 and Day 22,25,29,32.

B

Adriamycin	60mg/m^2 IV Day 1 and 22
Vincristine	1.4mg/m^2 IV (Maximum Dose 2mg) Day 1 and 22
Procarbazine	100mg/m^2 PO (Maximum Dose 200 mg) Day 1-10 and Day 22-31

C

Radiation Therapy

4000 rads/15 fractions/3 weeks beginning within 1-3 days of chemotherapy to encompass the primary tumor and regional lymph nodes.

2400 r/ 8 fractions/ 2 weeks to brain of responding patients beginning week 23

SCHEMA

Chest & Mediastinal RT (C)

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R A N D O M I Z E

CMC (A_1) ——— VAP, CMC, VAP alternating A_2 - B
(B) (A_2) (B)

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(B) (A_2) (B)

CMC = Cyclophosphamide, methotrexate, CCNU

VAP = Vincristine, Adriamycin, Procarbazine

Patients with progressive disease or no change at 12 weeks go off study.

Patients with progressive disease anytime after 12 weeks go off study.

1.0 Introduction

Small cell undifferentiated carcinoma (including oat-cell) differs considerably from other histologic cell types of bronchogenic carcinoma. Small cell carcinoma has the greatest metastatic potential of all lung cancer cell types. Regional and systemic spread generally occurs before disease recognition in the large majority of patients (1,2). Organs commonly involved by distant spread include the bone marrow (3,4), liver (5), brain (6), pancreas, adrenals and abdominal lymph nodes (7). Despite this high incidence of systemic metastases it is still useful prognostically (8) and therapeutically (9-14), to separate patients into limited and extensive disease categories. Limited disease is disease confined to one hemithorax including ipsilateral supraclavicular nodes, i.e. disease that can be encompassed wither a single radiation therapy port. Extensive disease includes contralateral lung involvement and any disease outside of the chest.

Small cell carcinoma is highly responsive to both chemotherapy and radiation therapy. Because small cell carcinoma disseminates early, chemotherapy is the principal therapeutic modality. Radiation therapy generally is used to control "bulk" disease and also to sterilize tumor within chemotherapy sanctuaries such as the brain. Previous studies indicate that combination chemotherapy is more effective than single agent treatment (15). Further intensive use of combination chemotherapy to significant hematologic toxicity gives better responses and survivals than more standard chemotherapy approaches. A previous NCI-VA study showed that when cytoxan, methotrexate and CCNU were given in conventional doses the response rate was 45% with no complete response. When the same drugs were given in high dose for 6 weeks the response rate was 96% with 30% complete responses. High dose chemotherapy was well tolerated. Since survival in small cell carcinoma is dependent on the completeness of response (9-14) it was not surprising that patients on high dose chemotherapy survived

determined whether chemotherapy alone or chemotherapy plus radiation therapy is the best treatment for limited small cell cancer we have developed a randomized study to test this question using our best chemotherapy with the radiation therapy dose, schedule and timing of Johnson and co-workers.

4.0 Randomization

4.1 Randomization will be performed by the Biometric Research Branch COP/DCT/NC

4.2 50% of patients will receive combined radiation therapy - chemotherapy for remission induction

4.3 The remaining 50% will receive only chemotherapy for remission induction

4.4 Chemotherapy induction is identical as regards drug doses and schedules in both groups

5.0 Treatment Programs and Duration

Drug doses will be calculated on the basis of body surface area using a height and weight nomogram and lean body mass for patients with edema.

5.1 Regimens

5.11 "A1" induction (CMC 6 weeks duration)

Cyclophosphamide 1500/mg/M^2 IV Day 1 and Day 22.

CCNU 100mg/M^2 PO Day 1

Methotrexate 15mg/M^2 PO Day 1,4,8,11 and Days 22,25,29,32.

5.12 "B" (VAP 6 weeks duration)

Vincristine 1.4mg/M^2 IV (maximal dose 2 mg) days 1 and 22.

Adriamycin 60mg/M^2 IV days 1 and 22

Procarbazine 100mg/M^2 PO days 1-10 and 22-31.

For the initial procarbazine course start at 50mg the first day, 100mg the second day and full dose by the 3rd day (Maximal daily dose 200mg). Maximum total adriamycin dose is 500mg/M^2.

5.13 "A2" (CMC maintenance 6 weeks duration).

Cyclophosphamide 500mg/M^2 IV days 1 and 22

CCNU 50mg/M^2 PO day 1

Methotrexate 10mg/M^2 PO Day 1,4,8,11 and day 22,25,29,32.

5.15.7 Localization (verification films and photographs of treatment portals will be obtained as of day #1 of external beam therapy: photographs will be permanently included in (1) raidation therapy chart· (2) hospital chart in order to evaluate results of treatment later.

5.15.8 Dosimetry monitoring will be done in each case on routine basis. Patients will receive chemotherapy as indicated in 5.11, i.e. regimen "A1" during radiation therapy.

5.16 Brain radiation therapy. All responders to treatment will will receive prophylactic brain radiation therapy 2400 rads/ 8 fractions 10 days beginning on week 24 of treatment.

5.2 Treatment Plan

5.21 All patients will receive high dose CMC (regimen "A1") for the first 6 weeks followed by VAP (regimen "B") for the second 6 weeks.

5.22 50% of patients will also receive radiation therapy to the primary lesion and to clinically involved hilar and mediastinal lymph nodes during the first 6 weeks of treatment.

5.23 Patients with no change or progression at 12 weeks go off study and may be treated on other appropriate protocols. If disease is still confined to the chest after restaging at progression, and if the patient has not received radiation therapy, the latter may be given.

5.24 Patients who develop progressive disease at any time after week 12 go off study.

5.3 Duration of treatment

5.31 Patients with a complete response will be treated for 52 weeks and then taken off all therapy and observed.

5.32 Patients with a partial response may be continued on treatment for the duration of response or may discontinue treatment after 52 weeks with concurrence of the study chairman.