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# Amphotericin B Plus Combination Chemotherapy for Extensive Non-small Cell Bronchogenic Carcinoma

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***Summary.*** *Sixteen patients with extensive non-small carcinoma of the lung were treated with methotrexate, vincristine, cyclophosphamide, and adriamycin. Cyclophosphamide and adriamycin were administered after pretreatment with amphotericin B. Amphotericin B-related toxicity was mild; cytotoxic chemotherapy-related toxicity was tolerable. The partial response rate was 12.5% and median survival was between 19 and 20 weeks. Response rate and survival were not superior to those of a similar drug combination lacking amphotericin B.*

## Introduction

Non-small cell carcinomas of the lung are common malignancies which are treated frequently with systemic therapy because of dissemination or because of progressive local disease despite surgery or radiation therapy. Response of such advanced lung cancer to chemotherapy is generally poor (roughly 10%–20% with single-agent chemotherapy, 20%–40% with combination chemotherapy), and the benefit of therapy as reflected by increased survival is small [9].

Amphotericin B has been postulated to improve the efficacy of a number of antineoplastic chemotherapeutic agents, presumably by increasing transport of drugs into tumor cells and thus overcoming one form of drug resistance. It has also been postulated that amphotericin B may have a salutary 'immunotherapeutic' effect [4, 7]. We have treated 16 patients with extensive non-small cell carcinomas of the lung with amphotericin B plus combination chemotherapy in an attempt to evaluate the putative ability of amphotericin B to enhance the effects of cytotoxic combination chemotherapy. The combination chemotherapy regimen included the drugs methotrexate, vincristine, cyclophosphamide, and adriamycin. This regimen was chosen to facilitate comparison with a group of patients treated with those same drugs (MOCA) at the same hospitals from 1975 through 1977 [8]. The dosage of drugs, however, was altered to decrease chemotherapeutic morbidity, and the schedule was altered to minimize or avoid toxicity related to possible diminished methotrexate excretion (secondary to potential amphotericin B nephrotoxicity).

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## Materials and Methods

Patients with extensive (metastatic beyond one hemithorax and ipsilateral supraclavicular nodes or recurrent in the field of past irradiation) non-small cell carcinoma of the lung were considered eligible for this protocol, with the following exclusions: age > 70 years, Karnofsky performance status < 5, brain or meningeal metastases, previous antineoplastic chemotherapy, previous radiation therapy involving > 25% of bone marrow-bearing sites, cardiac disease precluding the use of adriamycin, or creatinine > 1.6 mg/dl. Disease was staged by means of physical examination, chest radiograph, bone scan, and liver spleen scan.

Patients received therapy in 28-day cycles (Table 1). Amphotericin B was administered on days 1–4 in increasing doses (5 mg, 10 mg, 20 mg, 30 mg). It was infused IV, diluted in 500 ml 5% Dextrose in water, over 4–6 h after pretreatment with diphenhydramine 50 mg PO, acetaminophen 10 grains PO, and Solu-Cortef 50 mg IV. Adriamycin, 35 mg/m$^2$, and cyclophosphamide, 600 mg/m$^2$, were administered IV on day 4 1 h after completion of the amphotericin B infusion. Methotrexate 50 mg/m$^2$ and vincristine 1.4 mg/m$^2$ ($\leq$ 2 mg) were administered IV on day 22. Dosages of adriamycin, cyclophosphamide, and methotrexate were modified for hematopoietic toxicity. Doses of amphotericin B were delayed and doses of methotrexate adjusted or withheld for elevated creatinine. The dosage of adriamycin was adjusted for hepatotbiliary function: the dosage of vincristine was adjusted for neurotoxicity (Table 1). Repetitive studies included a CBC with differential and platelet counts on days 1 and 22, serum potassium and creatinine on days 1–4, screening chemistries (SMA-12), and chest radiograph at least monthly, and previously positive scans 2

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**Table 1.** Amphotericin B chemotherapy schedule

| Drug | Day | | | | |
|---|---|---|---|---|---|
| | 1(29) | 2 | 3 | 4 ..... 22 ..... 28 | |
| Amphotericin B[a] | 5 mg | 10 mg | 20 mg | 30 mg | |
| Cyclophosphamide[b] | | | | 600 mg/m$^2$ | |
| Adriamycin[b, c] | | | | 35 mg/m$^2$ | |
| Methotrexate[b, d] | | | | | 50 mg/m$^2$ |
| Vincristine[e] | | | | | 1.4 mg/m$^2$ ($\leq$ 2 mg) |

[a] Delayed 1 week for creatinine > 1.6 mg/dl or WBC < 3,000/mm$^3$
[b] Given at 50% level if WBC 3,000–3,999/mm$^3$ or granulocytes 1,000–1,499/mm$^3$ or platelets 75,000–99,000/mm$^3$; delayed 1 week if greater hematopoietic toxicity. Adriamycin and cyclophosphamide decreased to 75% if WBC nadir < 2,000/mm$^3$
[c] Given at 50% level for bilirubin 2–3 mg/dl, at 20% for bilirubin > 3 mg/dl
[d] Decreased to 25% level for creatinine 1.3–2.0 mg/dl, withheld for creatinine > 2 mg%
[e] Discontinued for paresthesias proximal to DIP joint or for manual or pedal weakness

months after initiation of therapy and then every 3 months or as otherwise indicated.

Complete response was defined as the disappearance of all evaluable disease. Partial response was defined as a 50% decrease in the sum of the products of the greater and lesser diameters of measurable lesions without the appearance of new lesions. Progression was defined as the appearance of new lesions or a 50% increase in the sum of the product of diameters of old lesions. In responders, therapy was administered until disease progression. In non-responders, therapy was administered until disease progression or for a maximum of three cycles. Survival is measured from the first day of treatment. All patients who received one or more doses of amphotericin B are reported.

On ten occasions serum amphotericin B levels were measured by bioassay (*Saccharomyces cerevisiae*) 1 h after completion of the day-4 amphotericin B infusion (at the time of adriamycin and cyclophosphamide administration).

Sixteen patients received treatment according to this regimen. All patients were males. The median age was 56 years. The median performance status (Karnofsky) was 8. Six patients had epidermoid carcinoma; eight had adenocarcinoma, and two large cell carcinoma. Common sites of metastases were distant lymph nodes (nine patients), bone (nine patients), liver (four patients), pleura (four patients), and soft tissue (two patients). Twelve patients had received prior radiation therapy. Three patients had disease confined to one hemithorax, which had progressed despite past radiation therapy.

## Results

### *Chemotherapy Received*

Three patients received only the amphotericin B, adriamycin, and cyclophosphamide portion of the first course of therapy. One of these patients died of his malignancy prior to day 22; the other two patients developed pneumonia (not related to leukopenia) prior to day 22 and had rapid tumor progression. The number of cycles of chemotherapy delivered ranged from 0.5–4, with a median and mean of 2. Ten of the 16 patients received two or more courses of therapy. Adjustments of drug dosage were made for hematopoietic, renal, or neurologic toxicity. The percentage of scheduled cumulative dosages delivered was 93% for both adriamycin and cyclophosphamide, 86% for vincristine, and 80% for methotrexate (doses not given because of discontinuation of protocol were not considered as scheduled).

### *Response Rates*

Two of the 16 patients (12.5%, 95% confidence range 0%–29%) had partial responses each lasting 3 months. One responder had epidermoid carcinoma metastatic to lymph nodes and liver. He died at 81 weeks after a secondary response to CCNU chemotherapy. The other responder had adenocarcinoma metastatic to bone and lung. He survived 31 weeks.

### *Survival*

Fifteen of the sixteen patients have died with survival ranging from 2–81 weeks. One patient is alive with active disease 84 weeks after starting therapy. Median survival time for the entire group is between 19 and 20 weeks and twenty-fifth percentile survival is 30 weeks. The estimated 95% confidence range for survival at 19 weeks is 25%–75%; at 30 weeks it is 4%–46%.

### *Toxicity*

Toxicity directly related to amphotericin B included fever (6/16), chills (8/16), mild transient renal toxicity

**Table 2.** Comparison of planned and delivered doses of myelosuppressive cytotoxic therapy in MOCA [8] and current regimen

| | Average dose/week | | | |
|---|---|---|---|---|
| | MOCA | | Current regimen | |
| | Planned | Delivered | Planned | Delivered |
| Methotrexate | 25/m$^2$ | 17.5/m$^2$ | 12.5/m$^2$ | 10 mg/m$^2$ |
| Cyclophosphamide | 250/m$^2$ | 175/m$^2$ | 150/m$^2$ | 140 mg/m$^2$ |
| Adriamycin | 15/m$^2$ | 10.5/m$^2$ | 8.75/m$^2$ | 8.3 mg/m$^2$ |

(creatinine 1.4–2.2 mg/dl; 6/16), hypotension (1/16), and abdominal cramps (1/11).

Toxicity related to the entire regimen included nausea and/or vomiting (13/16), alopecia (7/16), mucositis (3/16, 2 severe), and diarrhea (1/16). Leukopenia (< 2,000/mm$^3$, > 1,000/mm$^3$) was noted in two of the 16 patients. This may not reflect maximal hematopoietic toxicity, as blood counts were not routinely taken prior to day 22. No leukopenia-associated fevers or infection occurred. Three patients, however, developed pneumonia with adequate leukocyte counts. One patient developed a bowel infarction 12 days after receiving methotrexate and vincristine.

### *Amphotericin B Levels*

Serum amphotericin B concentration at the time of adriamycin/cyclophosphamide administration ranged from 0.77–1.55 μg/ml. The mean concentration was 1.03 μg/ml; standard deviation was 0.27 μg/ml.

## Discussion

Amphotericin B has been shown to enhance the efficacy of cytotoxic chemotherapy in a variety of preclinical systems. In mice with transplanted AKR leukemia, amphotericin B prolongs survival in animals treated with BCNU [4] or actinomycin D [11] and potentiates the cytotoxic effect (by spleen colony assay) of a variety of agents, most strikingly cyclophosphamide, nitrogen mustard, and adriamycin [10]. In tissue culture, amphotericin B enhances the cytotoxicity of actinomycin D against HeLa cells [5].

In clinical trials, amphotericin B combined with BCNU has shown promise [6]. It has also apparently abrogated drug resistance to the combination of adriamycin, BCNU, and cyclophosphamide in four of seven patients with malignancies refractory to that regimen [7]. Others, however, have shown only a limited ability of amphotericin B to reverse resistance to adriamycin-containing regimens in patients with breast cancer and sarcomas [3].

In a previous study, we treated patients with advanced lung cancer with MOCA (methotrexate, vincristine, cyclophosphamide and adriamycin) [8]. That regimen included the same antineoplastic chemotherapeutic agents as were used in this study, but at higher doses with a different schedule. The current regimen was scheduled to deliver 50%–60% of the doses scheduled for MOCA. Only 70% of the scheduled dosages of methotrexate, cyclophosphamide, and adriamycin could be delivered with MOCA. The current regimen involved delivery of 57% of the methotrexate delivered in MOCA, 80% of the cyclophosphamide, and 79% of adriamycin (Table 2). In those patients with non-small cell disease treated with MOCA, the response rate was 18% (9% for extensive disease) and median survival was 29 weeks (28 weeks for extensive disease). Response rates with other chemotherapeutic regimens including adriamycin and cyclophosphamide have been reported to be higher, in the 30%–40% range, but with similar survivorship [1, 2]. The results of the present study suggest that, while associated with tolerable toxicity, our amphotericin B plus chemotherapy regimen has failed to improve response rate or survival. While sample size and alterations in dosage and schedule from our previous MOCA regimen preclude firm conclusions about the specific impact of either amphotericin B or the altered dosage schedule upon these results, the response rate of 12.5% and median survival of 16–19 weeks were judged sufficiently poor to warrant discontinuation of the study.

Failure of amphotericin B as given in this study to demonstrably improve the chemotherapeutic effects of antineoplastic agents might not conflict with the preclinical data. Tissue culture systems have generally used concentrations of amphotericin B 20–30 times greater than the serum concentrations achieved

in this study. Studies in AKR mice have used 0.5–2 mg amphotericin B-dosages which, on a per square meter basis, are roughly 4–16 times the maximum daily dose given in this study. It is unclear whether or not amphotericin B, used at pharmacologic concentrations, would enhance chemotherapeutic efficacy in preclinical systems. While the toxicity of amphotericin B in this study was not limiting, it seems unlikely that levels equivalent to those used in preclinical studies could be easily achieved in man.

This study has failed to show a significant benefit from a chemotherapeutic regimen including amphotericin B. The regimen used, while tolerable, was ineffective and cannot be recommended.

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