UPDATE IN CANCER CHEMOTHERAPY, PART III: LUNG CANCER, PART 1

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An update in cancer chemotherapy that deals with the various therapies of lung cancer is described. At present, the stage of the disease and cell type are the major factors that determine the treatment. Important differences in the biological behavior and response to treatment exist between small cell and non-small cell cancers. The small cell type is sensitive to many chemotherapeutic agents. Differences in response to chemotherapy and survival have been less among the non-small cell types.

The treatment of non-small cell carcinomas including squamous cell, large cell, and adenocarcinoma are reviewed in Part I of this paper. Small cell lung cancer will be described in Part II, which will be published in a future issue of the journal.

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Lung cancer, the leading cause of cancer in the United States and many western countries, is continuing to rise in incidence. Among men it is the leading type of cancer, and among women it ranks third. In women, if present trends continue, it may surpass breast cancer and become the primary cause of cancer. In 1984, the American Cancer Society estimated there will be 139,000 cases with 121,000 deaths from lung cancer. This is roughly 25 percent of all cancer deaths.[1]

Cigarette smoking is considered to be the major etiological factor in 75 percent of lung cancer cases. Other causes are exposure to asbestos, ionizing radiation, dust, and chemicals such as arsenic, chromium, nickel, chloromethyl ester, coal products, mustard gas, and vinyl chloride.

While there are approximately 12 different histological types of lung cancer, 90 percent are called "bronchogenic carcinoma." The World Health Organization has divided the bronchogenic carcinomas into four major groups according to the cell type. These are squamous cell or epidermoid, small cell or oat cell, large cell carcinoma, and adenocarcinoma, which includes bronchiolar alveolar carcinoma.

Squamous cell carcinoma, the most common type reported, comprises 30 percent of the bronchogenic carcinomas. Some recent data

suggest that adenocarcinoma may now be more prevalent. Small cell carcinoma of the lung comprises 20 to 25 percent of bronchogenic carcinomas. The behavior of this tumor is vastly unlike the others because it usually grows rapidly, metastasizes early and widely, especially to the central nervous system, and has the poorest prognosis. It is the cell type most frequently associated with ectopic hormone production and with the paraneoplastic syndromes. The large cell carcinomas comprise 10 to 15 percent of the bronchogenic carcinomas. Approximately 30 to 35 percent of bronchogenic carcinomas are adenocarcinomas.

Lung cancers are grouped into three stages according to the TNM (tumor, nodes, metastases) system.[2,3] Table 1 shows the stages from I to III from good prognosis to bad prognosis.[4]

At present the stage of disease and cell type are the major factors that determine the treatment. Important differences in the biological behavior and response to treatment exist between small cell and the non-small cell cancers. The small cell type is very sensitive to chemotherapy. And in the past decade, the improved response rates and survivals in small cell lung cancer following the use of cancer chemotherapy represent one of the major advances in therapy. Differences in response to chemotherapy and survival have been less among the non-small cell types. Thus, the treatment of non-small cell carcinomas including the squamous cell, large cell, and adenocarcinoma should be considered separately from that of the small cell carcinomas. In general, the five-year survival rate of patients with bronchogenic carcinoma is from 5 to 10 percent.

NON-SMALL CELL LUNG CANCER

In the treatment of non-small cell lung cancer, surgery is the treatment of choice for operable and resectable tumors because it offers the best hope for cure. The first successful total pneumonectomy for bronchogenic carcinoma was performed on a physician by Graham in 1933.[5] In 1956, Watson summarized the Memorial Hospital experience of five-year survivors in lung cancer in 3,000 cases and concluded that "excisional pulmonary operation, when it can be successfully carried out, gives the patient a 25 percent chance of five-year survival.[6] In this series the cell type was related to resectability and curability. The least fatal type was the terminal bronchiolar alveolar cell lung cancer with 34 percent five-year survivors, followed by the epidermoid carcinomas with 26 percent five-year survivors. Among the adenocarcinomas, while 22 percent were resectable, the salvage rate was poor, and among the anaplastic or oat cell type, only 12 percent were resectable with only one patient surviving five years. Recent figures in 1981 in several series—Williams et al (Mayo Clinic)[7] and Melamed et al[8]—of non-small cell, stage I lung cancer show 80 to 90 percent, respectively, surviving five years after surgical resection.[7,8] In stage II, one third survived five years. The prognosis for adenocarcinoma and large cell carcinomas is poorer. Surgical resection of stage III non-small cell carcinoma of the lung produces 10 to 20 percent five-year survivals. In one recent series, Piehler et al[9] in 31 cases of $T_3N_0M_0$ reported a 54 percent five-year survival rate after surgical resections.

The developments in the use of radiation therapy in the treatment of lung cancer have been interesting. In 1933, Ormerod first reported some improvement in two patients with upper lobe lesions with the use of deep x-ray therapy.[10] In 1940, Leddy and Moersch reported in a study comparing 125 untreated lung cancer patients with 125 treated with radiation therapy. All of the untreated group were dead within one year and 20 percent of the irradiated group survived from 1 to 12 years. By the mid 1950s with the use of preoperative radiation, it was noted that early lung cancers were destroyed in the surgical specimens. Further studies demonstrated that radiation therapy provided increases in survivals comparable to the results of surgery in lung cancer.[11] However, two large randomized trials of preoperative radiation therapy showed no survival benefit from the radiation.[12,13] Postoperative radiation frequently employed has yet to be demonstrated in randomized trials to provide a survival benefit, yet regional control occurs with the use of radiation. In a study by Mountain et al,[14] most of the failures following

TABLE 1. STAGES OF LUNG CANCER

Occult Carcinoma	
$T_xN_0M_0$	Occult carcinoma with bronchopulmonary secretions containing malignant cells but without evidence of primary tumor or evidence of metastasis
Stage I Tumors Include	
TIS, N_0M_0	Carcinoma in situ
$T_1N_0M_0$	T_1 tumor, 3.0 cm or less in greatest diameter
$T_1N_1M_0$	Tumors are T_1 with nodes in ipsilateral hilar nodes only
$T_2N_0M_0$	T_2 tumor, more than 3.0 cm in greatest diameter and at least 2.0 cm distal to the carina. Any associated atelectasis or obstructive pneumonitis involving less than an entire lung with no pleural effusion
Stage II Tumors Include	
$T_2N_1M_0$	Tumors classified as T_2 with metastasis to the regional nodes in the ipsilateral hilar regional only
Stage III Tumors Include	
T_3 with any N or M	Any tumor more extensive than T_2. T_3 tumor any size with direct extension into adjacent structure, such as chest wall, diaphragm or mediastinum or involving main-stem bronchus less than 2.0 cm from carina. Any tumor associated with atelectasis or obstructive pneumonitis of entire lung or pleural effusion.
N_2 with any T or M	Any tumor with metastasis to the lymph nodes in the mediastinum
M_1 with any T or M	Any tumor with distant metastasis

postoperative radiation therapy were failures in distant metastatic sites. There have been decades of controversy over the use of radiation therapy in lung cancer. It is to be noted that there was a high rate of complications from radiation therapy in some of these studies.

In 1968, the Veterans Administration Lung Group conducted a large-scale randomized study of radiation therapy vs placebo in 800 patients with locally inoperable lung cancer.[15] The patients were randomized into three arms: (1) a radiation therapy group, (2) a placebo group and (3) a group where a variety of chemotherapeutic agents were administered. This study showed a statistically significant improved survival in one year in the group treated with radiation therapy, although it has been often misquoted.[10]

Adjuvant treatment of non-small cell lung cancer by local radiation after surgical resection is under investigation. In an attempt to improve the control of mediastinal node metastases in operable patients with disease limited to one hemithorax N_2M_0, a study of the value of perioperative brachytherapy with permanent iodine 125 implantation of the primary lung and a temporary iridium 192 implantation of the mediastinum with or without resection (followed by a moderate dose of postoperative external beam irradiation) was begun at Memorial Hospital by Hilaris et al in 1977.[16] In this study, local-regional control was observed in 76 percent of 88 patients. The median survival was 26 months and the two-year survival 51 percent. There was no postoperative mortality. In over 500 cases of nonresectable lung cancer

implanted with radioactive radon or iodine-131 seeds at thoracotomy, there were 19 five-year cures.[17]

In cases of unresected stage III non-small cell lung cancer, the standard treatment for many years was just radiation therapy. In this group only 5 to 10 percent survived five years following therapy. The value of radiation therapy in increasing the survival time in patients with non-small cell lung cancer (NSCLC) is not clear. It is questionable, except in very small lesions. In 1983 editorials, the controversy still persisted as to whether radiation therapy was indicated for all patients with NSCLC, some said, "yes" and some said, "no."[18,19] Radiation does, however, provide temporary palliation in NSCLC patients with the superior vena caval syndrome, obstructive dyspnea, hemoptysis, metastatic bone pain, and cerebral metastasis.

Because of the limitations of surgery and radiation therapy in effecting a cure for cancer of the lung, chemotherapy is being widely explored.

Single-Agent Chemotherapy in Non-Small Cell Lung Cancer

Single-agent chemotherapy has made little impact on patients with NSCLC. While temporary responses of a few months duration may occur, they are incomplete and not usually associated with improvement in the quality of life. In addition, survival times have not yet been significantly increased. Reported rates of objective tumor regressions with single agents have been variable and range generally from 5 to 30 percent. These agents include the alkylating agents, metabolic antagonists, plant alkaloids, antitumor antibiotics, metal compounds, and miscellaneous drugs.

Karnofsky and colleagues[20] first demonstrated temporary improvement in patients with lung carcinoma and tumor regression in those with the superior vena caval syndrome with the use of nitrogen mustard. When nitrogen mustard is followed by radiation therapy, 60 percent of patients with the superior vena caval syndrome will exhibit immediate relief. In the studies of single agents in the 1950s and 1960s response criteria were variable, cell types not always specified, and the reports more optimistic. In 1958, the Veterans Administration Lung Cancer Therapy Study Group began controlled trials of therapy on nonresectable primary lung cancer. In the first six protocols 3,351 patients were studied with one of the following treatments: nitrogen mustard, chlorambucil, cyclophosphamide, cortisone, diethylstilbestrol, testosterone, Δ^1 testalactone, fluoxymestrone, AB 132, placebo (an inert compound, lactose by mouth, or sodium chloride intravenously), or radiation therapy. In these six studies the mean survival of patients with nonresectable but still nonmetastatic disease was 134 days as compared with those with widespread disease who had a mean survival of 63 days. The value of concurrent controls was made clear in the study that demonstrated the deleterious effects of cortisone; these patients survived the shortest period of time. In this study neither radiation therapy or the alkylating agents had an effect on prolonging the lives of these patients.[21]

Among the difficulties in the evaluation of the effects of chemotherapy in lung cancer is the lack of well-defined measurable tumor masses in many cases where the disease is limited to the chest cavity. Shadows on lung x-rays are frequently deceptive as they may represent atelectasis, infection, fibrosis, or tumor. Compounding the problem of evaluation is that in some cases the disease appears to remain stationary for many months. Thus, survival time must serve as a most important criterion for improvement in the therapy of these patients. Newer diagnostic tools may help define chest tumor masses more precisely in the future.

Current criteria of response employed by the Working Party for Lung Cancer includes a 50 percent decrease in the size of measurable tumor in lung cancer, which is stricter than that presented in some reports. With the use of the newer criteria, Bodey et al,[22] reporting for the Working Party for Lung Cancer, achieved a 4 percent partial reponse rate in squamous cell lung cancer with cyclophosphamide. In a similar study, Vincent et al[23] at the Roswell Park Memorial Institute achieved a 5 percent partial response rate in squamous cell and a 6 percent response rate in adenocarcinoma of the lung with the use of varying dosages of methotrexate. In these studies dose schedules and extent of

disease were not the same as in previous studies. In a recent report by Djerassi and associates[24] with the use of high-dose methotrexate and equimolar citrovorum-factor rescue, there was a response in 23 of 51 patients (46 percent) with stage III NSCLC.

When strict criteria are applied in phase II studies, the alkylating agents—nitrogen mustard, cyclophosphamide, the nitrosoureas, the antimetabolites (methotrexate and fluorouracil) and the antibiotic, bleomycin—have response rates of under 10 percent. The more active single agents in NSCLC, more recently identified, have confirmed higher response rates in the range of 15 to 20 percent. These include cisplatin, mitomycin C, doxorubicin, vindesine, and etoposide. Table 2 shows the response rates of the most active single agents in NSCLC.

TABLE 2. ACTIVE SINGLE AGENTS IN NON-SMALL CELL LUNG CANCER*

Drug	No. of Patients	Objective Response Rates (%)
Cisplatin[27,28,29]	123	13-33
Mitomycin[30,31]	48	25-36
Doxorubicin[32]	288	15
Vindesine[33,34,35]	162	6-24
Etoposide[36,37,38,39]	93	4-18

*Adapted from Gralla RJ. Chemotherapy of lung cancer. In: Greenspan EM, ed. Clinical Interpretation and Practice of Cancer Chemotherapy. New York: Raven Press, 1982.

Combination Chemotherapy in Non-Small Cell Lung Cancer

Because of the successful use of polychemotherapy or combination chemotherapy in the treatment of leukemia, Hodgkin's disease, the lymphomas, germ cell carcinoma, and breast cancer, there have been grounds of optimism that the same approach would be useful in the management of NSCLC. In recent years the results of combination chemotherapy in NSCLC has been somewhat better, but the overall survival rates have not improved.

The initial combinations of drugs consisted mostly of the less active agents, especially the alkylating agents, cyclophosphamide (CTX) and the nitrosoureas in this tumor type. No significant benefit was noted in the following randomized trials conducted by large cooperative groups: CTX vs CTX+CCNU+HN_2 vs HN_2+CCNU; CTX vs CTX + VCR + MeCCNU + Bleo; CCNU vs Bleo vs CCNU + Bleo; MeCCNU vs MeCCNU + VCR vs MeCCNU + VCR + MTX; ICRF-159 vs VCR + Bleo + Adria; CTX vs CTX + CCNU, CTX + Adria, or CCNU + ADRIA. Response rates were low and no improvement in survival was noted. In some cases the single agent cyclophosphamide yielded an increase in survival as compared with the combination. In the large randomized Veterans Administration Lung Group study of 762 cases comparing CTX alone vs CTX plus CCNU, or CTX plus Adria, or CCNU plus Adria, there was a survival advantage for the combination of CTX plus Adria. Response rates were in the range of 4 to 5 percent. Toxicity was unacceptable with 20 to 25 percent of the patients treated experiencing severe life-threatening side effects.[5]

During the 1970s, other drug combinations employed in the treatment of NSCLC produced better response rates. The Southwest Oncology Group achieved responses in 40 out of 266 (17 percent) of cases treated with the combination popular in the treatment of breast cancer, namely CMFVP (cyclophosphamide, methotrexate, fluorouracil, vincristine, and prednisone).[25] In the author's investigations with CMFVP, responses were achieved in NSCLC without serious toxicity and no drug deaths by adjusting drug dosages to tolerance. More attention was given to the next group of drug combinations, which in initial trials produced even better responses in NSCLC. These included COMB (cyclophosphamide [Cytoxan], vincristine [Oncovin], methyl-CCNU, and bleomycin), BACON (bleomycin, doxorubicin, lomustine [CCNU], vincristine, and nitrogen mustard), NAC (nitrogen mustard, doxorubicin, and lomustine), MACC (methotrexate, doxorubicin, lomustine, and cyclophosphamide) and CAMP (cyclophosphamide, doxorubicin, methotrexate,

TABLE 3. CONVENTIONAL CHEMOTHERAPY: COMBINATION STUDIES IN NON-SMALL CELL LUNG CANCER

	Initial Trial		Repeat Trial		Median Survival (Months)	
	No. of Patients	Response Rate (%)	No. of Patients	Response Rate (%)	Whole Group	Responding Group
COMB[22,40]	58	24	20	5	2.5-3.5	4
vs						
Cyclophosphamide[40]	—	—	27	4	5	—
BACON[42]	50	38	98	21	3.5-5	7-9
vs						
NAC[41]	—	—	94	16	4	9
MACC[43-45]	31-68	39-44	43	12	4-8	6-11
CAMP[46,47]	23	48	51	27	6-8	12

COMB=Cyclophosphamide + vincristine + methyl CCNU + bleomycin; BACON=Bleomycin + adriamycin + CCNU + vincristine + nitrogen mustard; NAC=Nitrogen mustard + Adriamycin + CCNU; MACC+Methotrexate + Adriamycin + CCNU + cyclophosphamide; CAMP=Cyclophosphamide + Adriamycin + methotrexate + procarbazine.
*Adapted from Gralla, RJ. Chemotherapy of lung cancer. In: Greenspan EM, ed. Clinical Interpretation and Practice of Cancer Chemotherapy. New York: Raven Press, 1982

and procarbazine). Table 3 shows the results of these conventional chemotherapy combination studies in NSCLC.[26]

In Table 3 the initial reported trial is given for each of four studies as well as the follow-up trials.[27-38] It can be seen, as in single agent studies, that there is a broad range of activity with lower rates in the follow-up trials.

COMB, developed at the MD Anderson Hospital by Livingston et al,[40] included three different dose schedules used in sequential order—COMB 1, 2, and 3 in solid tumors including lung, head and neck, and melanoma. A total of 189 patients were included. There was a 6 percent mortality thought to be drug related and other disturbing toxicities such as myelosuppression, pulmonary fibrosis, and the "debilitating syndrome" consisting of weakness, anorexia, weight loss, and apathy. An anti-tumor effect was seen in 14 (24 percent) of 58 evaluable patients with NSCLC, but the overall survival time was not significant.

In the follow-up study reported in 1977 by Bodey et al for the Working Party for Lung Cancer,[22] COMB therapy was compared with cyclophsophamide in a randomized trial in advanced squamous carcinoma of the lung. Dosages of the drugs were adjusted according to toxicity and prior radiation therapy. Only one (5 percent) of 20 patients treated with COMB and one (4 percent) of 27 patients treated with cyclophosphamide achieved a partial response. Stable disease was noted in seven of the COMB patients and 13 of the cyclophosphamide-treated patients. In this trial COMB was not superior to cyclophosphamide.

The survival times of both groups was of short duration, although better for responders than nonresponders. Severe toxicity was observed in 65 percent of patients treated with COMB as compared with 19 percent treated with cyclophosphamide alone.

BACON, developed at the MD Anderson Hospital by Livingston et al,[42] also showed some encouraging response rates. Of 50 patients with NSCLC, tumor regression was observed in 17 (45

percent) of 38 with extensive disease and 4 (33 percent) with limited disease. Stabilization of disease was seen in 12 cases. Survival times of responders and those with stable disease were better than in nonresponders. There were a few drug-related deaths with BACON. The repeat trial of BACON compared with NAC by the Southwest Oncology Group[41] showed a lower response rate of 21 percent in NSCLC with BACON and only 16 percent with NAC.

MACC developed by Chahinian et al[43,44] at Mt. Sinai Medical Center showed an overall 44 percent response rate in NSCLC. However, in the repeat trial reported in 1979 by Vogl et al[45] for the Eastern Cooperative Oncology Group, the response rate was only 12 percent.

CAMP, developed by Bitran and associates[46] at the University of Chicago, was employed in 23 patients with NSCLC following radiation therapy. A 48 percent response rate (in 11 patients) was achieved. Because radiation was used, it is difficult to evaluate the effect of the drug. The median survivals were from 2 1/2 to 12 months, which is not significant when compared with survivals in the normal course of the disease in these cases. The repeat trial of CAMP by Lad et al[47] showed a 27 percent response rate. A lower response rate of 22 percent was obtained by the Eastern Cooperative Oncology Group with the CAMP combination.[48] In further studies, however, the overall confirmed objective response rate to CAMP in patients treated at several centers was 26 percent with complete responses in 6 percent.[26] In general, these so-called conventional combinations have had relatively little impact in the overall control of NSCLC with no significant increases in survival times.

The recent combination regimens containing platinum, mitomycin C, and the plant alkaloids (the vinca alkaloid and podophyllin derivatives)—drugs with important effects against squamous cell tumors and employed in NSCLC—are somewhat more promising. In 1977 Eagan and colleagues[49] (at the Mayo Clinic in a randomized crossover study of cyclophosphamide, doxorubicin, and cisplatin (CAP) vs dianhydrogalactitol (DAG) in untreated advanced non-small cell lung cancer) demonstrated a 39 percent overall regression rate with CAP I in 16 of 41 patients, but with no significant improvement in the median survival time. The cases included squamous cell, adenocarcinoma, and large cell carcinoma. Moderate myelosuppression was the major toxicity.

More recently Eagan et al in 1981[50] reported that in stage III unresectable NSCLC (with the disease confined to one hemithorax and the ipsilateral supraclavicular nodes treated with irradiation plus a combination of doxorubicin and platinum) a median survival of 11 months with 14 percent surviving three years was achieved. Others employing CAP combinations with higher doses of cisplatin and cyclophosphamide confirmed the observation of activity in NSCLC with overall response rates of 28 percent but with 35 percent remissions in previously untreated patients.[26,51-56] Complete responses occurred with CAP in only 1 percent of cases. Responding patients had a median survival of 16 months. The higher drug dosage used did not improve the response rates. When CCNU (lomustine) and vincristine were added to the CAP regimen (PACCO), a 66 percent response was seen in 35 patients.[57] However, another study using PACCO reported a lower response rate of 17 percent.[58] More recently in a comparison of the use of ACCO vs PACCO, the addition of platinum increased responses and nearly doubled survival one year from onset of therapy.[59] When etoposide was added to CAP, a 46 percent response was achieved in 28 patients.[60] The doses of CAP employed were cyclophosphamide, 400 to 600 mg/m^2, doxorubicin, 40 mg/m^2, and cisplatin, 40 to 100 mg/m^2 administered intravenously every 21 to 28 days.

The combination of cisplatinum and the vinca alkaloids or etoposide in NSCLC has produced objective remission rates in the reported range of 25 to 40 percent with complete response in 6 percent. In studies from Memorial Hospital by Gralla and associates,[61-63] two different dosages of cisplatin namely, 60 mg/m^2 vs 120 mg/m^2, IV, days 1 and 29, then every six weeks plus vindesine 3 mg/m^2, IV, day 1, every week for 6 weeks, then every 14 days were employed. There was a 46 percent response in 42 patients on the lower dose of cisplatin compared with a 40 percent response in 39 patients on the higher dose. Responding patients had a median survival time of 10 months on

the lower dose and 21.5 months on the higher dose of platinum.

In a four-year follow-up of patients treated with cisplatin and vinca alkaloids, Kris et al[64] in 1983 reported complete responses in 23 (8 percent). The patients with complete responses had mostly limited disease and median survival of 18 months (range 10 to 48 months). Ninety-six were alive in 12 months. Grohn et al[65] using a dose of 90 mg/m^2 of cisplatin plus 3 mg/m^2 of vindesine in a fairly similar intermittent schedule achieved a response rate of 50 percent in NSCLC.[65] With the use of the vinca alkaloid, vinblastine (5 to 8 mg/m^2) plus cisplatin (120 mg/m^2) in two recent studies, responses of 52 and 60 percent were reported.[66,67]

In other studies where platinum was administered with etoposide, response rates in NSCLC varied from 33 to 45 percent.[65,68-70] Thus far, the consistency of responses with the combination of platinum and the vinca alkaloids or etoposide has been greater than with other combination therapy in NSCLC.

The combination of vindesine and platinum produced emesis and neurotoxicity (generally peripheral neuropathy) in all cases treated.[63] The neurotoxicity subsided with the discontinuance of the vindesine. Other side effects noted were progressive anemia during therapy in 75 percent of cases. Alopecia in 66 percent, mild nephrotoxicity (creatinine over 1.4 mg/dL in 38 percent, leukopenia (white blood cell count less than 2,000 mm^3) in 19 percent, rare thrombocytopenia, hearing loss in 6 percent, mild constipation in 80 percent, and anaphylaxis. The anaphylaxis occurred ten minutes after the administration of platinum and consisted of erythematous cutaneous wheals, pruritis, respiratory distress, and mild hypotension. It was treated successfully in all cases with epinephrine or diphenhydramine. This hypersensitivity reaction is a known industrial problem among workers exposed to platinum. In contrast, the combination of vinblastine and platinum produced mainly marrow depression, probably mostly from the vinblastine, and nausea, vomiting, and nephrotoxicity from the platinum. The combination of etoposide and platinum produces similar side effects.

Combinations containing mitomycin C and the plant alkaloids have also yielded useful response rates in NSCLC in the range of 25 to 40 percent.[71] In recent studies the addition of platinum and other drugs to the combination has resulted in even higher response rates of over 50 percent. However, these studies await confirmation and the data on duration of response and survival are not yet available.

In the treatment of adenocarcinoma of the lung group of NSCLC, the mitomycin-containing combinations of interest include MAC (mitomycin C, doxorubicin, and cyclophosphamide), FAM (fluorouracil, doxorubicin, and mitomycin), FoMi (fluorouracil, vincristine, and mitomycin) and FeMi (fluorouracil, vindesine, and mitomycin). In a series of 28 patients with adenocarcinoma of the lung treated with MAC by Fraille et al,[72] there were seven (25 percent) partial remissions lasting 3.25 months. Median survival of responders was nine months vs four months for nonresponders. There were no responses in six cases of large cell carcinoma of the lung treated with MAC.

In a series of 25 patients with adenocarcinoma of the lung treated with FAM by Butler et al[73] from Georgetown University, there was one complete response and eight partial responses for an overall response rate of 36 percent. The responses lasted on the average for seven months. The median survival of the responders was 8.5 plus months and for the nonresponders, 2.5 months. There was moderate myelosuppression with the FAM regimen.

Rosi et al[74] employed escalated doses of FAM in a regimen called Hi FAM in 30 patients with adenocarcinoma of the lung and achieved one complete remission and nine partial remissions for an overall 33 percent response, which lasted 7.14 months. Responders had a median survival time of 10 plus months and nonresponders, 5.21 months. Hi FAM produced significant myelosuppression and two drug-associated deaths.

Miller et al[75,76] in a series of 56 stage III cases of adenocarcinoma of the lung treated with FoMi obtained a response in 23 (41 percent). Of the responses 19 were partial and four complete. Stable disease was noted in 12. In patients with large cell carcinoma of the lung treated with FoMi, there were four responses out of 10 for a 40 percent overall response; and in three patients with alveolar cell carcinoma treated with FoMi, there was

one response for a 33 percent rate. The FoMi combination was well tolerated. The major toxicity was nausea and in 14, after three courses of therapy, thrombocytopenia.

With the administration of FeMi, the Southwest Oncology Group obtained a 20 percent response (two complete remissions and six partial remissions) in 40 cases of adenocarcinoma of the lung and a 22 percent response (one complete remission and four partial remissions) in 23 cases of large cell carcinoma of the lung with a median duration of four months. The median survivals of the responders was 11 months and for the nonresponders five months.[77] In 1983 the Southwest Oncology Group reported that patients with NSCLC treated with alternating combinations of FoMi and CAP are surviving 60 percent longer than in any other previous SWOG study.[78] For FoMi there were 19 responders out of 23 patients; for CAP there were 21 responders out of 42 patients; and for FoMi/CAP there were 27 out of 46.

The most recent interest has been with combinations of mitomycin, the vinca alkaloids, and platinum, which are producing the highest response rates yet seen in NSCLC. In these initial reports, responses with the MVP combination range from 25 to 87 percent. Data on survival is yet incomplete and confirmation of the findings in larger numbers of cases is needed before concluding that this regimen is superior to others.

In 1980 Mason and Catalano[79] reported 53 percent remissions (two complete and 14 partial remissions) in 30 evaluable NSCLC patients treated with the combination of mitomycin, vinblastine, and platinum. Doses of mitomycin, 10 mg/m^2 plus vinblastine, 6 mg/m^2 and platinum, 40 mg/m^2, IV, every three weeks produced nausea and vomiting in most patients. Other observed side effects included diarrhea, paralytic ileus, chronic orthostatic hypotension, interstitial pneumonia, allergic reaction to platinum, life-threatening cytopenia in four and drug-related infectious deaths in two. Schulman et al[80] in 1982 with the use of MVP achieved a 25 percent (three partial remissions) response rate in 12 patients. Folman et al[81] in 1983 reported an 87.7 percent remission rate (five complete and 16 partial remissions) with the use of MVP in 28 patients.

In the two-year follow-up report in 49 patients with limited disease, the response rate was 77.7 percent.[82] In this investigation the MVP combination produced moderately severe marrow depression and two drug-related deaths (one suspected mitomycin lung toxicity and one sepsis and stroke). Chang et al[83] obtained a 55 percent (two complete and 10 partial remissions) response in 32 cases with MVP. In this phase I study the vinca alkaloid, vincristine, was used instead of vinblastine in the combination. The toxicity seen in this combination included pulmonary fibrosis, peripheral neuropathy, and marrow depression.

More recently reported were trials adding mitomycin to vindesine and mitomycin to vindesine plus cisplatin (MVP) in NSCLC.[84] In the Memorial Hospital study the response rate to M+V was 33 percent and to MVP, 52 percent. The M+V was well tolerated on an outpatient basis with little emesis. Late mitomycin lung toxicity in two, acute dyspnea in three, and renal toxicity in one patient were seen in the trial. A four-drug combination of mitomycin, methotrexate, vinblastine, and cisplatin produced a 55 percent response rate in 21 of 38 patients with acceptable toxicity and no drug deaths.[85] Further studies are necessary to determine whether these combinations of mitomycin, the vinca alkaloids, and platinum are the best.

Table 4 shows the results of combinations containing platinum, the vinca alkaloids, and mitomycin in NSCLC.

The most frequently employed combinations (confirmed to have consistent activity in NSCLC with response rates of 25 to 40 percent with complete remission rates of 5 to 10 percent and median survivals for responders of 12 months) are CAP, CAMP, FoMi,[86] and the plant alkaloids plus cisplatin. In these trials there have been 1 to 5 percent treatment-related deaths at the drug dosages employed.

In general, single agent therapy and the early combinations of drugs in NSCLC have had minor impact. The more recent combinations, however, are showing some improvement in response. While overall survival rates have not improved significantly, the data indicates that some of the platinum-based combinations are beginning to showe increases in survival. A major problem with the combinations thus far has been the excess

TABLE 4. RESULTS OF COMBINATION CHEMOTHERAPY WITH PLATINUM, PLANT ALKALOIDS, AND MITOMYCIN IN NON-SMALL CELL LUNG CANCER

Drugs	No. of Patients	Response (%)				Median Duration Survival (Months) Responders/ Non-Responders	
		Complete Remission	Partial Remission	Total	Range		
CTX+Adria+DDP (CAP)[49,51-56,60]	443	1	27	28	4-48	7-13	3.5-8
Plant Alkaloids (DVA, VLB, or VP-16) + DDP[63,65-67,69-70]	260	6		43	38-60	6-21.4	3.0-6
5FU + VCR+Mito C (FoMi)[75-76,86]	80	5	31	36	29-41	8	3.0
Mito C+(VLB,VCR, or VDB)+DDP[79-84]	183			58	25-87		
Mito C + MTX + VLB + DDP[85]	38			55			

*CTX—cytoxan; Adria—Adriamycin; DDP—cisplatin; Mito C—mitomycin C; DVA—vindesine; VCR—vincristine (Oncovin); VLB—vinblastine; VP-16—etoposide; MTX—methotrexate

associated drug toxicity and drug deaths. With skillful improvements in the dosage schedules and combinations, the benefits should outweigh the risks. Still the investigation of new agents remains a high priority in this area.

Table 5 shows the dose schedules of the most frequently employed combinations of drugs in NSCLC. Doses are modified if hematologic, neurologic, cardiac, or renal toxicity occurs.

Adjuvant Therapy of Non-Small Cell Lung Cancer

The adjuvant treatment of non-small cell lung cancer after surgical resection is under investigation. A study by McKneally et al[87] in American Joint Committee (AJC) stage I non-small cell lung cancer showed an increase in survival of those patients who received intrapleural bacillus Calmette-Guerin (BCG) postoperatively as opposed to those who did not. However, in 1981, the National Cancer Institute Lung Cancer Study Group reported no difference in survival in the two groups of stage I non-small cell lung cancer involving 400 patients with intrapleural BCG or a placebo after 516 days.[88] Numerous studies with single cancer chemotherapeutic agents employed as adjuvant therapy showed no benefit in NSCLC.

At present the Lung Cancer Study Group is comparing four different adjuvant studies as follows:[89]

1. AJC stage I non-small cell cancers (except T_1N_0) randomly divided into two groups: (1) No adjuvant therapy; (2) cyclophosphamide, doxorubicin, and cisplatin (CAP) for four cycles of therapy.

2. Stage II and stage III resected squamous cell lung cancer randomized into: (1) No additional therapy; (2) postoperative radiation therapy.

3. Stage II or III resected adenocarcinoma or large cell carcinoma of the lung randomized into: (1) Intrapleural BCG plus oral levamisole hydrochloride; (2) cyclophosphamide, doxorubicin, and cisplatin (CAP) for 6 cycles.

4. Patients with incompletely resected non-small cell lung cancers (NSCLC) randomized into: (1) Thoracic irradiation; (2) thoracic radiation plus 6 cycles of CAP.

Definitive answers from these four studies are

TABLE 5. DRUG COMBINATIONS USED IN THE TREATMENT OF NON-SMALL CELL LUNG CANCER

Drugs	Dosages
CAP	
Cyclophosphamide	400 mg/m² IV, day 1
Adriamycin	40 mg/m² IV, day 1 (total dose not to exceed 450 mg/m²)
Cisplatin	40 mg/m², IV, day 1 (with 1 liter 5% glucose in half normal saline over 1-2 hours)
Repeat cycle every 28 days	
CAMP	
Cyclophosphamide	300 mg/m² days 1, 8 IV
Adriamycin	20 mg/m² days 1, 8 IV (total dose not to exceed 450 mg/m²)
Methotrexate	15 mg/m² days 1, 8 IV
Procarbazine	100 mg/m² days 1-10 PO
Repeat cycle every 28 days	
FoMi	
5-Fluorouracil	300 mg/m², IV, day 1, 2, 3, 4
Vincristine	2 mg, IV total dose day 1
Mitomycin C	10 mg/m², IV, day 1
Repeat combination every 3 weeks for 3 courses, then every 6 weeks	
Vindesine and Platinum	
Vindesine	3 mg/m², IV, once/wk × 7, then every 2 weeks
Cisplatinum	120 mg/m², IV, with mannitol diuresis days 1, 29, then every 6 weeks

not available at present because the data are incomplete.

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