Chemotherapy of Lung Cancer

ROSE J. PAPAC, M.D.

Chief, Hematology/Oncology Service, Veterans Administration Medical Center, West Haven, Connecticut, and Associate Professor of Medicine, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut

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The potential for substantial improvement in the outcome of patients with carcinoma of the lung seems most likely to develop in the field of chemotherapy. In the past decade, striking advances in the management of small cell carcinoma have yielded higher response rates and longer survival. While the greatest improvement can be predicted for patients whose disease is limited in extent, combination chemotherapy and combined modality therapy generally are effective in causing tumor regression for the majority of patients. About 20 percent of patients with disease limited to the thorax and lymph nodes will survive two years.

In non-small cell tumors, response rates are improved with intensive drug combinations, although the majority of cases are unresponsive to present regimens. Careful staging and evaluation of patients indicates that patients with good performance status and limited extent of disease appear to obtain the most benefit from intensive treatment. The considerable morbidity of some treatments often influences the choice for or against chemotherapy in patients with non-small cell carcinomas.

For the future, problems of particular interest will be in investigation of factors—biologic, pharmacokinetic, immunologic—that are related to the failure to cure small cell carcinoma, the most therapeutically responsive pulmonary tumor. Additionally, in the non-small cell tumors, more effective therapies as well as clarification of the basis for relative resistance to cytotoxic agents are areas for intensive investigation.

In the treatment of lung cancer, chemotherapy has become a generally accepted and widely applied therapeutic modality. Since the majority of patients with this disease are not cured by surgery or radiotherapy, and also because many cases present with advanced stages of disease, chemotherapy is regarded as the most promising approach to the ultimate control of lung cancer.

In small cell tumors, significant advances in therapy have produced striking results [1–10]. The non-small cell tumors, however, have remained relatively refractory to treatment [11–15].

The premise upon which chemotherapy is based is that of eradication of tumor by cytodestruction. Optimally, effective therapy should demonstrate selective toxicity to tumor cells with little or tolerable damage to normal tissues. In practice, this has been difficult to achieve. Drug treatment has evolved, however, from empiric considerations of cell kinetics, the pharmacologic basis of antineoplastic agents, and metabolic aspects of tumor growth [16–18].

In the past decade, the use of two or more antineoplastic agents, simultaneously or in close succession, has proved highly effective in diseases such as acute leukemia,
Hodgkin's disease, and breast cancer [19-22]. The rationale for combination chemotherapy is based upon the concept that the effectiveness of antitumor agents may be enhanced by concurrent and sequential inhibition of metabolic pathways for DNA biosynthesis [23], which could yield additive or synergistic effects. Additionally, it is possible that the use of multiple agents, by analogy to antibiotic usage in the management of infectious disease, could reduce the development of drug resistance [24]. In actual clinical practice, however, combinations of drugs are generally selected on the basis of known effectiveness of each component drug in the disease and divergent toxicity of the component drugs.

Despite the widespread use of combination chemotherapy, relatively little attention has been given to possible detrimental results. Drug interactions could prove to be antagonistic, so that agents, known to be effective when used singly, would become ineffective in combination. There is also the potential for ineffectiveness of a known active compound, when used in combination, due to the dose-response requirements of the individual agent. Combinations generally include doses lower than those used when compounds are administered singly. Certain agents, to be effective, may require higher doses to elicit a response than those doses employed in combinations. In the design of clinical trials with drugs in combinations, consideration of these possible adverse effects is merited.

NON-SMALL CELL CARCINOMA

In evaluating antitumor response in patients with non-small cell carcinoma, the effectiveness of treatment may be assessed in relation to cell type and stage of disease (Table 1) [11]. Factors such as performance status, complicating illness, and age are important determinants in the outcome [25,26].

Early studies with single agent chemotherapy in cases with advanced disease suggested generally low response rates in patients with epidermoid carcinoma and a

| Drug                  | Epidermoid | Small Cell | Adeno. | Large Cell |
|-----------------------|------------|------------|--------|------------|
| CCNU                  | + +        | +          | + +    | +          |
| Mechlorethamine       | + +        | + +        | +      | +          |
| Methotrexate          | + +        | +          | + +    | + +        |
| Procarbazine          | + +        | +          | + +    | +          |
| Cyclophosphamide      | + +        | + + +      | +      | +          |
| Adriamycin            | +          | + +        | +      |            |
| 1-ME-1-Nitrosourea    | +          | + +        | +      |            |
| Bleomycin             | +          | 0          | +      |            |
| Hexmethyimelamine     | +          | + +        | +      | +          |
| Mitomycin C           | 0          | 0          | + +    | +          |
| Platinum diamminodichloride | + + | + + | 0 | 0 |
| VP-16-123             | 0          | + + +      | 0      | 0          |
| 5-Fluorouracil        | +          | 0          | 0      | +          |
| Vincristine           | 0          | + +        | 0      | 0          |
| Vindesine             | +          | 0          | 0      | 0          |
| m-AMSA                | 0          | 0          | +      | 0          |

+ + +, response > 40 percent of all patients
+ +, 20 percent-39 percent
+, 10 percent-19 percent
0, < 10 percent
negligible rate of response in patients with adenocarcinoma arising in the lung [27].
Subsequent compilation of results of treatment show great variability in response
rate. To some extent this is a consequence of differing criteria in evaluating response,
as well as small numbers in individual series. Often the determination of response in
pulmonary lesions is based upon indirect measurements—the chest X-ray lesion may
be a manifestation not only of tumor but of associated infection, inflammation, and
perhaps bleeding. There are certainly major areas of serious question regarding
efficacy of treatment with cytotoxic drugs in non-small cell carcinoma.

Recent data is based upon greater uniformity in assessment with respect to staging
and criteria for response. There is a trend toward multi-modality intensive treatment
of patients with locally unresectable non-small cell tumors [28,29]

A recent approach to the management of inoperable cases of lung carcinoma has
been to combine chemotherapy with “reductive” surgery; that is, to surgically remove
tumors following regression with chemotherapy. Preliminary data are encouraging
[29]. Reducing the bulk of the tumor is theoretically advantageous as a means of
rendering additional cytotoxic therapy more effective.

In patients with non-small cell carcinoma with advanced disease, various drug
combinations are reported to induce tumor regression considered superior to that
achieved with single agents, although few controlled trials comparing single agents to
drug combinations have been carried out. Laing [30], in a randomized study, found
that combination chemotherapy was associated with shorter median survival than
single agent therapy or a control group (untreated), but better symptomatic control
of the disease developed in survivors of combination chemotherapy.

Intensive therapy with drug combinations generally yields response rates higher
than those reported in the past. However, responses are seldom complete. Survival
times vary from three to ten months, and rarely exceed one year [31-37]. An
exception is the trial of Egan et al. in which median survival of 17 months was
achieved [28].

Table 2 summarizes data from some recent selected clinical trials in non-small cell
carcinoma of the lung. It is apparent that high response rates in some series are not
verified in subsequent trials involving larger numbers of patients [12,34,35,38].
Additionally, there is often serious morbidity and occasional lethal complications
associated with intensive therapy. Nevertheless, numerous other regimens are in the
process of clinical trial or reporting in an attempt to find therapies of greater benefit
and less toxicity.

Preliminary studies with newer agents, vindesine, m-AMSA, the acridine dye
derivative 4'-9-acridinylamino-methane-sulfone-M-anisidine, and maytansine suggest
that they may exert anti-tumor effects in non-small cell carcinoma [42-45].
Vindesine is being included in current trials of combined therapy for lung neoplasms
[39].

In randomized and in sequential trials, there does not appear to be a clear
advantage for intensive treatment of non-small cell carcinoma of the lung, as
compared to single agent therapy [13,14,30]. Careful staging and evaluation of
factors that influence response rate appear to identify patient groups who benefit
from treatments—those with limited extent of disease and good performance status.

Non-small cell tumors remain unresponsive to chemotherapy in the majority of
cases. In the individual patients, the very considerable morbidity of treatment
(although tolerable in most instances) must be a major factor influencing the choice
for or against chemotherapy for this disease.
## TABLE 2
Recent Results of Treatment of Non-Small Cell Carcinoma of the Lung

| Treatment | No. of Patients | Cell Type | Response | Median Survival (months) | Toxicity |
|-----------|-----------------|-----------|----------|--------------------------|----------|
| CTX, A, P, TRT [28] randomized with | 27 | adeno | 15/27(1CR) | 17 | leucopenia 25/34, thrombopenia 5/34 |
| CTX, A, D, TRT | 28 | adeno | 12/28(2CR) | 7 | leucopenia 25/34, thrombopenia 6/34, cardiotoxicity 1/60, nausea, vomiting 68/68, renal toxicity 12/68 |
| TRT [25] versus | 21 | adeno | NA | 6 | nausea, vomiting 15/38 |
| TRT and Hu, CCNU | 79 | squam | NA | 7 | leucopenia < 3,000/10/38 |
| M, A, CTX, CCNU [12] (MACC) | 20 | adeno | 1/43 | 3 | leucopenia < 1,000/11/43, thrombopenia < 25,000/5/43, stomatitis 3/43, liver dysfunction 2/43, lethal outcome 2/43 |
| M, A, CTX, CCNU [38] (MACC) | 12 | adeno | 3/12 | 7* | leucopenia < 2,000/15/30, cardiotoxicity 1/30, lethal outcome 2/30 |
| CTX, A, Mi [31] (MAC) | 30 | adeno | 7/30 | 9* | leucopenia < 2,000/10/30, nausea, vomiting 14/30, stomatitis 6/30 |
| CTX, A, M, F [33] | 18 | adeno | 7/18(3CR) | 7 | leucopenia, life threatening 4/48 |
| CTX, A, P, V [34] (CAPV) | 15 | squam | 6/6/1(1CR) | 9 | nausea, vomiting 35/35, diarrhea 15/35 |
| M, A, CTX, CCNU, V [36] (MACCV) | 9 | adeno | 3/9 | 7 | leucopenia < 2,000/15/30, lethal outcome 2/30 |
| CTX, A, P, V [35] (CAPV) | 2 | adeno | 0/2 | 6 | nausea, vomiting 12/18 |
| | 12 | squam | 3/12(1CR) | 6 | leucopenia < 1,000/2/18, thrombopenia < 25,100/1/18, lethal outcome 1/18 |
TABLE 2—Continued

| Treatment | No. of Patients | Cell Type | Response | Median Survival (months) | Toxicity |
|-----------|----------------|-----------|----------|-------------------------|----------|
| CTX, CCNU, M [44] | 56 | adeno | 8/56 | 5 | thrombopenia 12/88 |
| | 32 | large cell | 6/32 | 5 | |
| A, P | 56 | adeno | 4/56 | 4 | thrombopenia, life threatening 13/76 |
| | 21 | large cell | 1/21 | 4 | leucopenia, life threatening 1/76 |
| CTX, Fu, CCNU [26] | 23 | adeno | 5/23(1CR) | 9 | nausea, vomiting 5/23 |
| | | | | | leucopenia < 1,000 7/31 |
| | | | | | thrombopenia < 100,000 20/31 |
| Fu, Mi, V [37] | 43 | adeno | 17/43 | 6 | vomiting 4/56 |
| | 10 | large cell | 4/10 | | thrombopenia < 100,000 14/56 |
| | | | | | leucopenia < 3,000 7/56 |
| | | | | | lung toxicity 1/56 |
| | | | | | lethal outcome 2/56 |
| HEXA, Mi [39] | 24 | not specified | 4/24 | 5 | thrombopenia < 100,000 6/24 |
| | | | | | nausea, vomiting 3/24 |
| | | | | | stomatitis 1/24 |
| | | | | | lethal outcome 1/24 |
| CTX, P, Vi [40] | 29 | adeno | 8/29 | | renal toxicity 9/24 |
| | 6 | squam | 2/6 | | nausea |
| CTX, A, P [41] | 43 | adeno | 13/43 | 9* | life threatening |
| | 39 | squam | 12/39 | 4** | toxicity 12/90 |
| | 26 | large cell | 8/26 | | |

*responders only; 'limited disease; **extensive disease
NA = data not available; CTX = cyclophosphamide; A = adriamycin; P = cis platinum; TRT = thoracic radiotherapy; D = DTIC; HEXA = hemamethylmelamine; Hu = hydroxyurea; Fu = fluorouracil; M = methotrexate; F = folinic acid; V = vincristine; Vi = vindesine; Mi = mitomycin; CR = complete response; adeno = adenocarcinoma; squam = squamous cell carcinoma

SMALL CELL CARCINOMA

Small cell carcinoma, once considered one of the most rapidly lethal neoplasms of man, is the type of pulmonary carcinoma most responsive to cytotoxic therapy. Single agents, notably alkylating agents, are effective in inducing tumor regression in about 25–30 percent of cases, although responses are generally brief [11,27]. As in other neoplastic diseases, current trends are toward intensive treatment regimens, including use of multiple drugs, cyclic treatment of from six to 24 months' duration and combined modality usage, with both radiation therapy and chemotherapy.

Concomitant with increased interest in the therapeutic management of small cell carcinoma has been the development of sophistication in defining the extent of the disease and assessing the impact of clinical parameters upon the outcome. The predominant factor affecting survival appears to be the extent of disease at the time of diagnosis [1,46]. Patients who have disease confined to the thorax and adjacent
lymph node sites are considered to have limited disease. With one exception [47], clinical studies demonstrate improved survival for patients with limited extent of disease, as compared to those cases with more disseminated disease, classified as extensive stage of disease. Attempts to identify factors other than extent of disease that may influence prognosis have not been definitive. Recent publications suggest that patients with cerebral metastasis have better survival than those with other metastatic sites [48]; patients with bone marrow involvement and particularly those with associated peripheral blood cytopenias have shortened survival [49]. Patients with a solitary extra pulmonary focus of metastasis may have a more favorable outcome than those with widespread metastases [50].

Numerous drugs have demonstrated significant antitumor effects in small cell carcinoma of the lung (Table 1) [1,11]. Following the demonstration of the effectiveness of alkylating agents, the use of cyclophosphamide following radiation treatment to the primary tumor was assessed to determine whether survival could be favorably influenced [51]. Subsequently, drug combinations came into widespread clinical use as a consequence of studies in small numbers of cases suggesting increased response rate and longer survival [52,53]. Most of the clinical trials utilized survival data from published reports—few controlled studies with less intensive regimens and single agent treatment have been carried out. Nevertheless, the results achieved with intensive therapeutic regimens are impressive, as reviewed by Greco et al. [9] (Table 3).

In a randomized study reported in 1975 [54], Laing compared a four-drug combination to the use of radiotherapy in patients with both limited and extensive

| Regimen | Patients (n) | Median Survival (wk) | One-Year Survival (%) | Reference |
|---------|-------------|---------------------|-----------------------|-----------|
| No specific therapy | 31 | 14 | 7 | [14] |
| Surgery* | 270 | – | 19 | [16-19] |
| Radiotherapy* | 235 | 25 | 20 | [5,20-22] |
| Radiotherapy plus | | | | |
| 1 CTX† | 27 | 31 | 38 | [21] |
| 2 CTX, VCR† | 23 | 50 | 50 | [23] |
| 3 CTX, VCR, ADR† | 108 | 52 | 50 | [25] |
| 4 CTX, VCR, ADR BCG† | 19 | 78 | 70 | [28] |
| 5 CTX, VCR, ADR‡ | 16 | 76 | 80 | [35, 36] |
| 6 CTX, VCR ADR‡ | 32 | Not reached | 75 | [9] |

*Mean values of several studies
†Radiotherapy given after starting chemotherapy or “sandwiched” between chemotherapy
‡Radiotherapy given concomitantly with chemotherapy. CTX — cyclophosphamide; VCR — vincristine; ADR — doxorubicin (Adriamycin); BCG — Bacillus Calmette Guerin
stages of small cell lung carcinoma. In this trial, the morbidity of the radiotherapy patients was related to the metastatic disease; in the chemotherapy patients, there was symptomatology related to the primary tumor. He suggested that optimal treatment could be a judicious combination of both modalities. In practice, most trials recently have utilized this approach. For patients with limited extent of disease, the median survival is generally from 14 to 18 months; it is estimated that 20 percent of such cases will survive two years [1].

The combined modality approach includes “prophylactic” cranial irradiation so designated because the rationale is to prevent the development of cerebral metastases. In two reports [55,56], this procedure has not been effective, but generally the incidence of brain metastasis is diminished in patients receiving cranial irradiation early in the course of management [57]. Recently, low dose abdominal irradiation has been included in combined modality regimens, but its role is to be determined [56].

Drug combinations that are generally used in small cell carcinoma may include from two to six agents. The use of six agents simultaneously appears to offer no therapeutic advantage [58]. Whether the use of alternating combinations will reduce the development of drug resistance and prolong survival has been assessed by several investigators without clear evidence of benefit.

There has been an attempt to define the optimal number of cycles needed to achieve maximum response, and it appears that there is no advantage associated with more than six drug cycles [59]. Presently, in the combined modality approach, drug treatment precedes and follows radiotherapy to the primary tumor [60]. Cranial irradiation is often administered during the thoracic treatment.

Despite these innovations in management, little improvement has developed in survival or response rates. The morbidity of increasingly intensive treatment is significant, so that some of the assumptions regarding the efficacy of this approach are being questioned [61].

A recent controlled trial comparing single agent chemotherapy (cyclophosphamide) with irradiation to combination chemotherapy with irradiation in both limited and extensive stage disease found no survival difference in the groups [62]. The response rates were higher in the limited disease cases, however. The observations are consistent with our own findings.

Seventy patients referred to the oncology service at the West Haven Veterans Administration Hospital, over the past decade, were studied to determine the survival in relation to different types of therapy. Median survival for the entire group was 221 days. Of 23 cases who received solely radiotherapy (having refused additional treatment), median survival was 212 days, although a single patient survived eight years and two months. Of 18 patients treated solely with single agent chemotherapy, median survival was 231 days and a single case survived four years three months after cyclophosphamide treatment. In 35 cases given six cycles of combination chemotherapy with cyclophosphamide, vincristine, and methotrexate in addition to thoracic irradiation, median survival was 276 days. The differences are not statistically significant.

Despite generally improved survival outcome for cases with limited extent disease, few patients seem to be cured of the disease. Indeed, careful scrutiny for metastatic or residual disease, will probably yield evidence for lesser degrees of response—periodic bronchoscopy suggests this [63]. It is unclear at this time whether the present approach and recent innovations will ultimately succeed in achieving cures or whether a plateau of responsiveness has developed.

The reasons for failure to achieve cure are presumed to be related to the
development of resistance to therapy. If this is correct, then the use of multiple agents and alternating forms of cyclic agents may be extremely important. The development of more effective and varied cytotoxic agents could lead to control of the disease.

On the other hand, if the tumor, as Yesner [64] has postulated, arises from a cell lineage capable of differentiation toward other cell lines, it is possible that drug resistance is not the sole reason for failure to control the disease. Morphologic differentiation to other cell types—squamous and adenocarcinoma—may result in tumor cells unresponsive rather than resistant to treatment. Following therapy, as well as prior to treatment, morphologic evidence of multiple cell types is well documented [65].

Another possible mechanism in small cell carcinoma could be related to the tumor model studied by Fidler [66]. Within the tumor, clones with variable metastatic potential exist. Treatment could enhance or diminish tumor cell lines with selectivity for sites and numbers of metastatic foci. Therefore, patients with limited extent of disease have a biologically favorable form of the disease as compared with those with extensive disease and treatment per se is not the most important determinant of outcome.

The elucidation of biologic events in the course of treatment, that is, differentiation, drug resistance, and host factors, will probably be the most significant factors leading to ultimate control of the disease.

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