Heme Oncol

SMALL CELL LUNG CANCER:
A PROBLEM OF TUMOR HETEROGENEITY

MEDICAL GRAND ROUNDS
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Lung cancer represents the leading cause of cancer deaths in males (35%) and it is predicted that in 1986, it will exceed breast cancer in females in that respect (19%). The two primary avenues via which this major cause of mortality will be eventually reduced will be through decrease in the use of tobacco products as well as developing techniques to identify those individuals particularly prone to develope the disease. Almost certainly, the pathogenesis of lung cancer involves an interaction between environmental carcinogens and promoters and a genetic predisposition to undergo the critical mutations.

At the present, however, the clinician is faced with the problem of treating this large group of patients with the intent of palliation, or, in a distinct subset of patients, cure. For purposes of treatment decisions as well as a foundation for clinical therapeutic trials, lung cancer is presently approached as two groups of disorders: small cell undifferentiated lung cancer (SCLC) and the non-small cell lung cancers (NSCLC) which include squamous cell, adeno-, and large cell undifferentiated carcinomas. This division has occured primarily due to differences in clinical behavior and also presumed differences in histogenesis. Clearly, most patients with SCLC have a disease which tends to be more disseminated at diagnosis, has a shorter tumor doubling time and is more likely to be responsive to chemotherapy and radiation therapy than NSCLC types. Exceptions to these points exist in a minority of patients in either group. As will be discussed, there may very well be biologic correlates to explain the heterogeneity of lung cancer between patients. In addition, laboratory investigation and clinical observations have led to a reconsideration of the concept that the cell of origin of SCLC is different that that for NSCLC (1).

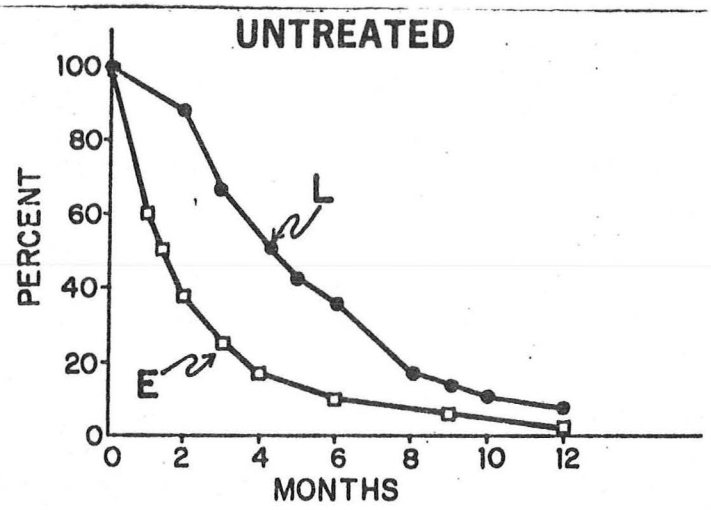
For purposes of this review, we will attempt to elucidate the present status of the clinical management of patients with a histologic diagnosis of primary lung cancer of the small cell undifferentiated type.

In the early 1970's, it became apparent that the natural history of SCLC could be altered by non-surgical therapeutic modalities, and that a definite subset of patients could be cured of this disease. Treatment trials from the mid-1970's have reached full maturation and the long term impact of such treatment can be analyzed. In addition, it is possible to begin to evaluate other parameters such as optimal chemotherapy regimens, the role of radiotherapy, prognostic subgroups with a better potential for cure, anatomical patterns of failure and long term toxicity of treatment.

Early large VA cooperative group studies in lung cancer delineated the natural history of SCLC when untreated or managed with ineffective therapy (2,3). An initial observation was that SCLC patients could be prognostically divided into those who had clinical evidence for metastatic disease beyond the confines of one lung and the mediastinum - extensive disease (ED) - and those in whom clinical evaluation demonstrated only local disease with or without regional lymph node metastases - limited disease

(LD). (Figure 1). Median survival times from diagnosis for these two groups, when untreated, were approximately 6 weeks and 4 months respectively. One year survivals were rare in ED and less than ten percent

FIGURE 1. Natural History of SCLC



in LD. A summary of multiple early chemotherapy trials are shown in table 1.(4). It was initially believed that a period of two years free of relapse was tatamount to cure. It is now clear that that is not the case and that relapses continue to occur, not infrequently, between two and three years, and occasionally after three years (5-8). Recently, two groups have

TABLE 1.

OUTCOME OF STANDARD CHEMOTHERAPY OF SMALL CELL LUNG CANCER

STAGE	CR (%)	CR+PR (%)	MEDIAN SURVIVAL (MOS)	2YR DFS (%)
LIMITED				
NO TREATMENT	--	--	5	0
CHEMOTHERAPY	50	80	10-14	7
EXTENSIVE				
NO TREATMENT	--	--	1.5	0
CHEMOTHERAPY	25	67	7-10	2

CR = Complete response; PR = >50% decrease in all lesions;
DFS = Disease free survival

reviewed their long term followup data of early trials and their results are summarized in table 2 (5,6). It is of interest to note that the five year survival rate in the LD patients was greater than for two years in the combined chemotherapy trial data. All of the patients in the SWOG study who achieved a chemotherapy response received thoracic radiotherapy (essentially 100% of the long term survivors) and 10 of 14 long term survivors in the NCI

TABLE 2.

LONG TERM FOLLOWUP OF TREATMENT OF SCLC

GROUP	YRS OF ENTRY	STAGE	#PATIENTS	% 5 YR+ SURVIVAL
NCI	1973-78	LD	103	11.7
		ED	149	1.3
		ALL	252	5.6
SWOG	1974-76	LD	103	10.7
		ED	273	2.2
		ALL	376	4.6

studies received chest radiotherapy. Clinical trials from this period have served as a means for evaluating patterns of failure and as a background upon which to design potentially more effective therapeutic strategies. Table 3 lists a number of factors which appear to impact upon therapeutic results and towards which clincial and laboratory studies are being directed.

TABLE 3.

FACTORS EFFECTING THE OUTCOME OF TREATMENT
OF SMALL CELL LUNG CANCER

STAGE OF DISEASE
BIOLOGIC HETEROGENEITY
HISTOLOGIC HETEROGENEITY
THERAPEUTIC MODALITIES
- CHEMOTHERAPY
- RADIATION THERAPY
- SURGERY

CENTRAL NERVOUS SYSTEM RELAPSE

THE BIOLOGY OF SMALL CELL LUNG CANCER

A number of investigators have begun to explore the biology of lung cancer by a variety of techniques employing fresh tissue or continuous cell lines derived from lung cancer specimens. These types of studies have opened new avenues of research into the in vitro characterization of these malignancies which hopefully will produce strategies of therapeutic attack that are innovative. Two primary patterns have emerged from these observations: 1) SCLC possesses several unique features that differentiates it from NSCLC and 2) heterogeneity is remarkable. Not only does SCLC from different patients display variations from the typical pattern, but in some circumstances, rare or occasional NSCLC may exhibit certain features that are usually demonstrated only by SCLC. Actually, these patterns of overlap in several areas between SCLC and NSCLC as well as certain pathologic data (see section on pathologic diagnosis) have led to a reassessment of the traditional concept that SCLC and NSCLC arise from different stem cell compartments (1). Several of these biologic features are listed in table 4. SCLC lines generally show certain features including various neuroendocrine markers such as dopa decarboxylase activity (9), neuron-specific enolase activity (10-12), production of peptide hormones (13), neurosecretory granules (14), as well as specific cytogenetic abnormalities (15) and the production of the BB isoenzyme of creatine kinase (16). Of particular importance is the recognition that a rare or occasional NSCLC line may demonstrate one or more of these features (9-12).

TABLE 4. COMPARATIVE BIOLOGY OF LUNG CANCER CELL LINES

FEATURE	SCLC-C	SCLC-V	NSCLC
Culture Morphology	Classic	Variant	Attached
Mean cloning efficiency(%)	2	14	--
Mean doubling time (hrs)	79	32	--
Mean DDC (units/mg)	199	<1	--
Bombesin/GRP (pmol/mg)	4	<1	<1
NSE (ngm/mg)	1495	481	<100 *
CK-BB isozyme (ng/mg)	6488	5055	~20% lines
3p- chromosome	All	All	0
Bombesin receptors	+	+	0
Bomb. stim mitogenesis	+	+	0
Monoclonal Ab binding:			
Anti-Leu 7 (>50% cells)	75%	50%	0 *
Anti- glycoprotein Ab's	High	Low	--
Anti-EGF receptor	0	0	+
Anti-neurotensin	+	?	0
c-myc amplification	Rare	Common	Rare
Radiosensitivity:			
Do (rads)	51-140	80-91	--
n (repair factor)	1.0-3.3	5.6-11.1	--
% survival 200 rads	6-32	56-58	--

DDC=dopa decarboxylase; NSE=neuron specific enolase; * expressed in occasional line; EGF=epidermal growth factor

Dr. John Minna and his collaborators have established over fifty separate SCLC cell lines in culture and/or nude mouse xenografts. It is especially relevant that in their studies these lines continue to express all of the genetic information, including morphology, of the original lesion through many passages. Although 70% of the lines possess all of the classical features of SCLC (SCLC-C), approximately 30% differ in selected characteristics, the "variant" cell lines (SCLC-V) (10,17). These differences include such parameters as growth patterns in culture, more rapid doubling times, higher cloning efficiency in agar, loss of DDC, loss of bombesin-like immunoreactivity (BLI), reduction in NSE content, different patterns of surface glycoprotein antigens (18), Leu-7 antigen expression (19), radiation sensitivity (20), and different forms of intermediate filament proteins (21). All SCLC cell lines appear to be deficient in HLA antigen expression as well as in the production of B_2 microglobulin (22). This heterogeneity is further emphasized by the observation that some SCLC-V lines demonstrate the biochemical differences of SCLC-V but not the culture growth pattern differences (17). As one might speculate, these inter-class differences between lines appear to have some clinically relevant correlations such as survival differences (see section on pathologic diagnosis). Two other features of SCLC lines are of particular interest and serve as potential targets for therapeutic manipulation. Minna's group and others have demonstrated that an analogue of the amphibian peptide, bombesin, is found in SCLC tissues and cell lines (23,24). Receptors for this peptide (in humans called gastrin releasing peptide, GRP) are found on SCLC cells but not NSCLC cells. Even thought the SCLC-C lines lose cytoplasmic BLI, they continue to express the receptors (25). Both in culture and in nude mouse xenografts, bombesin-GRP behaves as an autocrine growth factor which can be inhibited by a specific antibody (26,27). In addition, anti-idiotypic antibody to the anti-bombesin antibody appears to produce effects that would be predicted for an antibody to bombesin-GRP receptors. Other preliminary data from Minna's laboratory suggests that a family of peptides may be coded for by the GRP gene, some or all of which may possess growth factor properties. The second observation has been that increased expression of certain oncogenes may be, with rare exceptions, specific for SCLC as opposed to NSCLC. The c-myc oncogene is amplified in the majority of SCLC-V lines up to a 76 fold increase and is associated with a parallel increase in c-myc RNA production (17,28). This has been correlated with the presence of double minute chromosomes and/or homogeneous staining regions on cytogenetic analysis. In some cases, where c-myc gene amplificaiton has not been found, the gene product has been increased and evidence for gene translocation or rearrangement has been demonstrated. The increased c-myc expression has been found predominantly and, almost exlusively, in the SCLC-V lines. Transfection of SCLC-C lines with c-myc gene copies results in the line acquiring many of the characteistics of SCLC-V (29). Additionally, other oncogenes of the myc family - n-myc and L-myc have been shown to be amplified in some non c-myc amplified lines, particularly SCLC-C lines (30). At present, 21/33 SCLC lines have demonstrated some increase in myc family oncogene expression. Rarely, increased c-myc expression has been found in NSCLC lines. Early clinical data indicate that increased c-myc expression may be associated with a more aggressive clinical behavior which seems to correlate with the variant morphology and altered growth patterns in vitro of SCLC-V. Clearly, these studies provide exciting areas to pursue that could potentially lead to innovative therapeutic approaches.

PATHOLOGIC DIAGNOSIS

Traditionally, by light microscopy, primary lung cancer is divided into four predominant histologic subtypes. The relative frequency of these forms is shown in table 5. SCLC respresents 20-25% of these tumors which translates into nearly 10% of all cancer related deaths in males and 5% in

TABLE 5.

HISTOLOGIC CLASSIFICATION OF LUNG CANCER

CELL TYPE	FREQUENCY %
SQUAMOUS CELL CARCINOMA	25-40
ADENOCARCINOMA	20-30
LARGE CELL UNDIFFERENTIATED	10
SMALL CELL UNDIFFERENTIATED	20-25
MIXED TUMORS	?
OTHER	1

females. For management purposes, primary lung cancer is divided into SCLC and NSCLC types. Accurate diagnostic distinction between these two groups is therefore of major importance for determining treatment modalities and prognosis. Serveral lines of study have demonstrated problems in diagnosis and classification of tumors along these pure and traditional lines (31). Such problems include inadequacy of pathologic material. The flexible fiberoptic bronchoscope frequently provides only small tissue specimens. Improper handling of specimens may lead to artifacts. Cytologic specimens may be the only source of material for diagnosis (sputum, bronchial washings and brushings, effusions, fine needle aspirates etc.). Although there is generally good interobserver agreement on cell type diagnoses from such specimens, the limited number of cells available tend often to be unrepresentative of the tumor when a larger amount of tissue is avialable. The specificity of cell type diagnosis by cytology or from small specimens may be in the order of 75-85% (32). Mixed tumors (see below), atypical carcinoids as well as "small cell" variants of NSCLC may be misdiagnosed because of these factors. Our own experience in patients with LD SCLC has demonstrated a significant difference in response rates depending upon the source of material and the confidence of the pathologic diagnosis made therefrom (table 6).

TABLE 6.

RESPONSE RATE IN LIMITED SCLC RELATIVE TO PATHOLOGY DIAGNOSIS

TISSUE DIAGNOSIS	#	MAJOR RESPONSES %		
		CR	PR	TOTAL
DEFINITE SCLC (BIOPSY)	26	58	35	93
DEFINITE SCLC (CYTOLOGY)	7	29	27	56
PROBABLE SCLC	9	22	44	66

As indicated in the section on the biology of SCLC, significant heterogeneity of biochemical and morphologic features among specimens and cell lines exists as well as overlap of features in some cases of NSCLC. One clinical counterpart to these observations is the phenomenon of mixed cell types of lung cancers. When larger volumes of tumor are available for examination (eg. surgical specimens or autopsy tissue) a significant number of lung cancers are found not to have a pure histology. A study of 100 patients found that only 34% of such specimens were homogeneous and 21% had only a minor additional cell type. Thus 45% were significantly mixed tumors. Eight of 15 SCLC were admixed with a significant NSC component (33). Rebiopsies from relapsing SCLC patients have demonstrated other morphology in 20% of patients and autopsy studies have shown either SC-NSC tumors or only NSC lesions in 24-39% of cases (34). Of particular relevance in this regard, several recent prospective studies which have evaluated the use of adjuvant surgical resection following chemotherapy have demonstrated a significant proportion of the residual disease to contain mixed or pure NSC histologies (35-42) (table 7).

TABLE 7. Strict criteria = Major tumor response required prior to surgery.

SURGICAL PATHOLOGY FOLLOWING CHEMOTHERAPY

GROUP	PATHOLOGY	# PATIENTS	% PATIENTS
All Patients	No Tumor	18	20.5
	SCLC	54	61.4
	NSCLC	11	12.5
	Mixed	5	5.7
Strict Criteria	No Tumor	12	30.8
	SCLC	26	66.7
	Mixed	1	2.5

Previously, SCLC was classified into subtypes (oat cell, intermediate, fusiform). Several studies have demonstrated that these divisions have no relevance to clinical presentations or response to treatment (43-45). The "oat cell" sub-type probably represents hypoxic/degenerative changes in the true or intermediate form (31). However, one mixed type, often included in the intermediate sub-type of SCLC, is the admixture of classic SC and large cell undifferentiated components. This has been termed the #22/40 variant (46). Two separate studies have demonstrated that this variant has a clinically inferior behavior to therapy, both in terms of response and survival compared to typical SCLC (43-44). (Table 8). This subtype appears to be the clinical correlate of the SCLC-V in the studies from Minna's group. It grows in cell culture with the variant pattern and in nude mouse xenografts as the mixed or 22/40 morphology. As noted above, this variant has different biochemical and growth characteristics from SCLC-C lines and is also more radioresistant (17-20).

TABLE 8.

RESPONSE AND SURVIVAL OF CLASSIC AND VARIANT SMALL CELL LUNG CANCER - ALL STAGES

CELL TYPE	#	MAJOR RESPONSES (%) CR	PR	TOTAL	MEDIAN SURVIVAL (mos)
CLASSIC SCLC	256	38	47	85	10.0
MIXED SC-LCLC	46	17	41	58	5.8

Clearly, one important lesson derived from these observations is that the most tissue possible should be obtained for cell type diagnosis. An additional approach to this dillema has been to attempt to apply other histologic techniques to cytology or biopsy material to differentiate SCLC from NSCLC. Electron microscopy has been utilized. Squamous cell and adenocarcinomas have typical ultrastructural features in most cases (46a). The neuroendocrine counterpart by E.M. of classic SCLC is the presence of neurosecretory or dense core granules (NSG). However, several studies have shown that only 30-70% of specimens of SCLC demonstrate NSG. In large part, the failure to detect NSG'S is a function of the quantity and handling of the tissue (31). Histochemical and immunocytochemical studies utilizing cytoplasmic or membrane antigens or markers to differentiate SCLC from NSCLC are presently being evaluated for ease of application and reliability. These include stains for neuron-specific enolase (11,12,47), heterologous or monoclonal antibodies to bombesin (24), Leu-7 antigen (19), and membrane antigens specific for SCLC and NSCLC (48-50). These approaches hold promise for reaching more accurate cell type diangoses.

CHEMOTHERAPY IN SCLC

Chemotherapy is the most important treatment modality for SCLC. A number of single agents or classes of drugs are active against this tumor including alkylating agents (especially cyclophosphamide), Adriamycin, periwinkle alkaloids (especially vincristine), VP-16, cis-platinum, methotrexate, nitrosoureas, procarbazine, hexamethymelamine and bleomycin. Single agents alone were intially shown to impact slightly upon survival, but the major progress, including potential for cure, was first appreciated when combination chemotherapy regimens were employed (4). However, the results in terms of response rates, survival times and numbers of persons with long term disease free survivals reached an apparent plateau in the

late 1970's (51). Evaluation of these initial studies has identified a number of factors which appear to limit the eventual outcome from this modality. A variety of approaches have been or are being explored to attempt to overcome these barriers to curative chemotherapy.

Vascular supply - solid tumors often have a limiting blood supply which impairs direct exposure of some tumor cells to adequate cytotoxic concentrations of drug. Alternate or additional approaches to eradicating this "bulky" disease have been to employ othe modalities in concert with chemotherapy such as irradiation and/or surgery (see below).

TABLE 9.

RESULTS OF "INTENSIVE" CHEMOTHERAPY OF EXTENSIVE STAGE SMALL CELL LUNG CANCER

REGIMEN	MAJOR RESPONSES (%) CR	PR	TOTAL	MEDIAN SURVIVAL (MOS)	% 2 YR DFS
STANDARD Rx	10-20	30	40-50	6-10	<5
HD CAV	24	51	75	9.7	~5
HD CVC	57	14	71	8.3	?
HD ECHO	52	48	100	12	~4
HD VCAV	24	70	94	12	~6
HD C-VP	44	50	94	10	?

Sanctuary sites - certain anatomical areas are frequently sites of early and often clinically inapparent metastases, but eradication of these micro-metastases is prevented by a failure of drug access. For SCLC, the problem is primarily in the CNS where the blood brain barrier (BBB) prevents adequate diffusion of the most effective agents for this tumor. The brain, meninges or extradural space of the spinal cord are a frequent site of failure in patients in whom all other clinical evidence of tumor has resolved. Methods employed to attempt to overcome this problem include prophylactic whole brain irradiation, prophylactic intrathecal chemotherapy and early spinal radiation prophylaxis (see below). Techniques of temporary disruption of the BBB are also being explored (52).

Drug concentration - it is clear that at least some chemotherapeutic agents demonstrate a dose-response effect in some tumors. Thus, potentially greater cell kill and even a higher frequency of permanent cytoreduction might be appreciated by utilizing regimens in which one or more of the drugs are given in higher doses. To date, unfortunately, high intensity regimens, both single agent and combinations have not demonstrated a major impact upon curative outcome when administered "up front" even though, in some studies,

the initial response rates and median survival times may be marginally improved (53-57) (table 9). These results have been at the cost of considerably greater toxicity including more treatment related deaths. One problem with this approach is that the majority of the active agents in SCLC have myelosuppression as at least one of their dose limiting toxicities. In order to try to overcome this limitation to high intensity treatment, investigators have employed autologous bone marrow "rescue" to shorten the duration of severe B.M. suppression. Using this as an initial induction approach has not been rewarding (58-61). One mathematical model of cancer chemotherapy predicts that intensive therapy would be most important when there is only minimal residual disease (62). A recent trial utilizing this concept has provided the most promising results in this area. The intensification of treatment along with autologous BM support was given after conventional courses of chemotherapy induction. Five of 13 patients who achieved a complete clinical remission prior to the intensification cycles have continued in continuous complete remission for a period of three or more years. (63) (table 10). However, for this approach to have an impact on a greater number of patients, a greater increase in major cytoreduction with conventional induction regimens would seem a necessary prerequisite. An additional approach which is in the initial exploration stages is the concept of targeted drug (or radiation) delivery, eg. utilizing toxins, chemotherapy agents or radionuclides conjugated to tumor specific monoclonal antibodies (64).

TABLE 10. Spitzer et. al. J. Clin. Oncol. 4:4 (1986)

Autologous Bone Marrow Transplantation in Small-Cell Bronchogenic Carcinoma: Survival With High-Dose Intensification

Response		Survival (Months)			Patients Response*	
Induction	Intensification	No.	Median	Range	Disease Free	(Months)
CR	CR	13	23	6–59+	33+, 48+, 51+, 58+, 59+	12
PR	CR	9	16	6–37+	37+	6
PR	PR	10	9	5–28	—	5
Overall		32	14	5–59+	—	11

*Median calculated from time of maximal response.

Toxicity-A primary limiting factor to utilization of chemotherapy is toxicity. The first approach to this problem was to employ drug combinations with components that produce different toxicities allowing additive therapeutic effects without additive toxicity. This was the primary concept of combination chemotherapy and provided the initial important advances in the drug therapy of a number of malignancies, including SCLC. Although new agents have been developed which have different mechanisms of action, they tend to share similar toxicities and therefore larger numbers of drugs given concurrently have not significantly impacted upon long term outcome and toxicity has been greater (53,53a).

Drug Resistance - Unquestionably, this is the single most important factor impairing the curative outcome of chemotherapy. It also represents one of the best examples of tumor heterogeneity, both within a given tumor as well as between tumors of the same cell type from different patients (65). Preliminary studies have shown that there is a broad range of patterns of drug sensitivity and resistance between SCLC specimens tested in cultured cell lines and xenografts (83-85). These studies, as well as observations in patients receiving intensive treatment regimens, suggest that drug resistant cells emerge early following induction therapy in SCLC (58).

Experimental models as well as clinical observations indicate that prior to any therapy, a given tumor will be composed of a number of heterogeneous cell populations of variable size in terms of drug sensitivity phenotype: a) tumor cells without any drug resistance, b) cells with resistance to one drug or class of drugs, c) cells resistant to more than one drug or class in which the multiple resistance required separate mutational events and d) cells resistant to more than one drug of unrelated structure in which resistance occured as a consequence of a single mutation, the so called multiple drug resistance phenotype (66-69). At a given point in time in the natural history of a tumor, the frequencies of these various types of drug resistant cells has been shown experimentally to be a function of tumor growth rate (doubling time) and the rate of spontaneous mutations to the various resistance patterns (66,67). Therefore, slower growing tumors will tend to have a greater degree of drug resistance relative to the total number of cells, and larger tumors will tend to have more drug resistance relative to smaller tumors with similar growth rates. This latter concept may explain, in part, the clinical prognostic correlations of response and survival with parameters denoting tumor burden such as performance (or functional) status, number of metastatic sites, levels of tumor derived markers or products such as serum LDH, and differences in prognosis between LD and ED patients (70,71). These concept of resistance are compounded by further features of tumor cell heterogeneity. Experimental data in certain animal tumor systems suggests that cells with a higher intrinsic metastatic potential are more likely to possess a drug resistance phenotype (65,72). Clinically, this may correlate with those patients who have ED, but in whom the apparent tumor burden is low, yet are less responsive to treatment than LD patients with comparable tumor burdens.

Despite the complex mechanisms and mathematical considerations of development of drug resistance, one unequivocal conclusion can be drawn regarding the ability to cure a malignancy with chemotherapy alone: all of the cells in the primary tumor and its metastases which possess the capacity of self renewal (tumor stem cells) must be susceptible to kill by at least one drug, at clinically tolerable doses, used in the treatment, and all such cells must be eradicated prior to the mutation of any one tumor stem cell to resistance to all drugs employed.

A number of possible solutions exist which attempt to overcome the pervasive problem of drug resistance. These include:

1. Use more drugs in the initial combination which possess different mechanisms of action and therefore potentially do not share the same resistance mechanisms. The limitations of this approach, due to intolerable toxicity, have been mentioned above.
2. Develope new drugs with unique mechanisms of action and without cross-resistance to other agents. Recently, two such drugs have been introduced into the management of SCLC and early observations have demonstrated promising potential (see below). The development of other new agents is a continuing avenue of research. Particularly pertinent to SCLC is that screening of drugs that may be effective in this tumor is being carried out on cultured cell lines and xenografts established from SCLC tumors which should enhance the selectivity of the screening process.
3. Employ drugs concurrently which demonstrate synergism rather than just additive effects. This explains, in part, the particularly effective combination of cyclophophamide, Adriamycin and vincristine (CAV) which is basically the benchmark for established drug combinations in this disease. At least the first two drugs appear to be synergistic in several tumors. More recently, two other agents, the podophyllotoxin, VP-16 and cisplatinum, each of which has some single agent activity in SCLC, have been shown to be synergistic in some animal tumor systems (73). At the clinical level, they appear to be synergistic in a number of human tumors, and remarkably so in SCLC (74-79). Response rates in previously untreated patients appear to be at least equivalent to those with CAV (75,76). An additional important feature of this two drug combination (VP-P) is that it demonstrates the first clear example in SCLC of a regimen with true non-cross resistance to CAV (74, 79). In patients who have failed to respond to or have relapsed after a response to CAV, introduction of VP-P produces additional major responses in a significant number of patient. (table 11). Because both of

TABLE 11. Ref. 74,75.

RESPONSE TO PLATINUM + VP-16 IN SMALL CELL LUNG CANCER

		NO PRIOR TREATMENT			
STAGE	# PTS	MAJOR RESPONSES (%)			MEDIAN SURVIVAL
		CR	PR	TOTAL	(MOS)
LIM	11	64	18	82	15
EXT	17	29	59	88	9

		PRIOR CAV THERAPY			
STAGE	# PTS	PRIOR CAV RESPONSE	MAJOR RESPONSES (%) CR	PR	TOTAL
LIM	16	YES	19	69	88
	8	NO	13	37	50
	24	BOTH	17	58	75
EXT	26	YES	8	50	58
	28	NO	0	46	46
	54	BOTH	4	48	52

27% OF PATIENTS HAD SUPERIOR RESPONSE TO P-VP THAN CAV

these agents produce myelotoxicity as a limiting problem, mere addition to CAV concurrently is not feasible. An alternate strategy is described below.

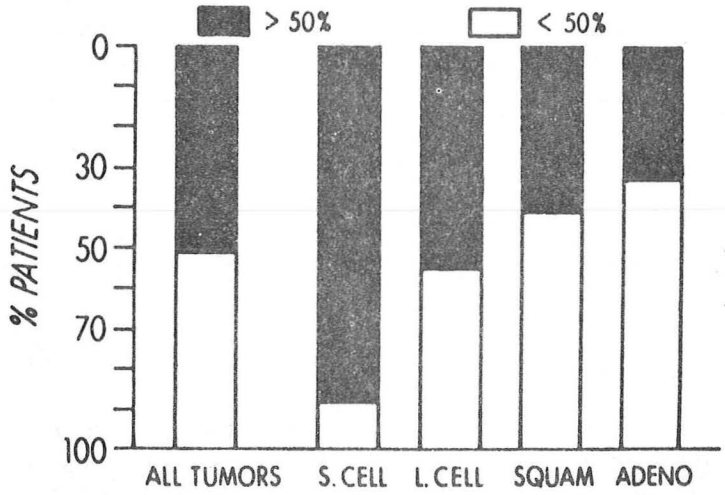
4. Goldie and Coldman have developed computerized mathematical models which permit the testing of concepts of drug resistance utilizing a variety of variables such as growth rate, rates of mutation to drug resistance and combinations of drug resistance phenotypes (66,67). They have tested the question of optimal scheduling of non-cross resistant chemotherapy drugs or combinations. This model assumes that in a certain mathematically predictable proportion of tumors (based on doubling times, mutation rates and tumor burden) all tumor stem cells are initially sensitive to one or both non-cross resistant therapies. If the two types of drug resistance are nearly proportionately balanced, the model predicts that the optimal use of the two therapies would be alternating them after each course as opposed to more sequential schedules of alternation. Prior studies of alternating non-cross resistant chemotherapy in SCLC have not shown much success (80,81). These trials suffered from one or both of two problems - lack of evidence of tru non-cross resistance of the combinations employed or scheduling one comibination for several cycles before switching. The Goldie-Coldman data would predict a failure of such therapy to improve significantly upon the results using only one of the combinations until failure or relapse. It is of interest that two initial studies which used CAV and VP-P did so by switching to the second regimen only after 4 or more cycles of the first. No improvement in CR was noted (76,77). One non-randomized study alternating CAV and VP-P with each cycle in previously untreated patients produced a 67% CR rate and a 95% overall major response rate (78). If confirmed, this represents a clearly more effective result from chemotherapy alone than presently exists. Parenthetically, the Goldie-Coldman model would suggest that this response rate may be approaching a limiting maximum for this strategy. Also, early results from a cooperative group trial in LD patients which employs rapid alternating CAV and VP-P combined with thoracic radiotherapy demonstrates an impressive CR rate (70%), 2 year disease free survival rate. (35%) (82)

5. Another approach with a high theoretical potential and supported by some clinical data is to individualize drug regimens based upon in vitro chemosensitivity testing of tumor cells obtained from each patient. At present, technical problems severely limit this approach to initial therapy. Tumor stem cell cloning techniques as well as cell culture and nude mouse xenograft methodology have been investigated (83-85). The ability to establish a sufficient number of colonies (cloning efficiency) from tumor specimens to test a large number of drugs and concentrations at first limited the stem cell assays to only a small percentage of attempts. Cell culture techniques have a higher success rate and appear to correlate well with sensitivity patterns derived from cloning methods. The present barrier is the time necessary to obtain results (up to 12 weeks) and, therefore, chemosensitivity testing cannot be presently used to direct chemotherapy choices at the time of diagnosis.

THE ROLE OF THORACIC RADIOTHERAPY IN SMALL CELL LUNG CANCER

SCLC is frequently radiosensitive, particularly when compared to NSCLC. When tumors are exposed to 4000 rads or greater, more than 80% of the time a regression exceeding 50% will occur (fig. 2) (86). The heterogeneity of

FIGURE 2. Ref. 86



this cell type is also noted with regard to this aspect as well. Not all regressions are complete and, nearly 20% of the time, little or no regression occurs. Similar heterogeneity of radiation sensitivity has also been demonstrated in vitro (20). Nevertheless, total tumor eradication is potentially possible if sufficient doses can be delivered to a given mass. There does appear to be some dose-response relationship. In one study, local control clinically occured 60% of the time with a dose of 3000 rads(r) and this increased to 88% with 4800 r (87). CR rates in a SWOG combined modality study were significantly different in patients receiving 3000 r (32%) as opposed to 4500 r (57%). This study also showed that dosage errors resulted in inferior local control rates compared to patients who received the radiation therapy (RT) as designed (34% versus 69%) (88). An autopsy study showed that approximately 33% of patients who had received a dose of 4800 r or greater had total eradication in the irradiated field (89). Rare cases of irradiation induced cure have been documented (90). Clinically, a complete response has been demonstrated with RT alone at a dose of 4500 r in 30% of patients. Another 44% had a greater than 50% reduction of tumor mass (91). Three reasons make RT an inappropriate primary therapy alone. The complete response is less than with chemotherapy alone in LD. In part, this is due to technical problems preventing delivery of therapeutically optimal doses without unacceptable toxicity. Secondly, SCLC is, in the vast majority of the cases, a systemic disease and early systemic progression occurs after RT alone. Finally, significant delays in chemotherapy to await the RT outcome is often accompanied by a greater incidence of chemotherapy resistance due to the time factor.

On the other hand, there are a number of theoretical reasons and clinical observations that suggest that the addition of RT to chemotherapy might have an overall greater benefit than chemotherapy alone. There is no direct correlation between chemosensitivity and radiosensitivity of a given tumor (20). Bulky masses may be more amenable to radiotherapy than chemotherapy because of problems of drug access. A third potential benefit would be that the known radiation sensitizing effects of certain chemotherapy compound might enhance the overall tumoricidal effect of a dose of radiation. Thus, where systemic control may be accomplished by CT, including potential eradication of micrometastiatic sites, bulky disease might require additional modalities for tumor elimination. Clinically, certain observations support this contention. Radiation therapy given after progression of disease has minimal impact in terms of further response (92). However, RT given early to patients who have achieved a PR in the chest often results in conversion to CR (93,94). The long term followup data from the NCI and SWOG trials demonstrated higher 5 year survival rates than have been recorded for chemotherapy alone at two years. (5,6). In both cases, all long term survivors in the SWOG study and the vast majority of such survivors in the NCI series, radiation therapy was part of the treatment program. A review of all early published clinical trials of combination chemotherapy with or without radiotherapy demonstrated that although the complete response rates were similar, the two year disease free survival was greater than twice as high in those protocols utilizing radiotherapy (7% versus 17%) (4). From a number of non-randomized studies, it is clear that the first site of clinical failure after complete remission in LD is in the local-regional site in the majority of patients treated with chemotherapy alone. This is true whether the data is expressed as the total number of CR patients who relapse first in the chest or as the proportion of relapses which occured in the chest (to correct for different overall relapse rates in various series) (tabel 12) (81,95-100). Thus, combined modality

TABLE 12.

LOCAL RECURRENCE IN LIMITED STAGE SMALL CELL LUNG CANCER

TREATMENT MODALITY	% WITH LOCAL RELAPSE	% RELAPSES THAT ARE LOCAL
Chemotherapy Only	50-70	70-90
Chemotherapy + Radiation	20-50	40-60
Surgical Resection[1]	6	13
Resectable: CT + RT only[2]	42	58

1 48% of patients relapsed

2 73% of patients relapsed

treatment seems to be superior to chemotherapy alone in terms of duration of local-regional control. The primary question, however, is whether, with the more recent improvements in chemotherapy protocols, this superior local-regional control will translate into a greater proportion of long term survivors, since systemic relapse is the predominant problem in combined modality treatment. In the past few years, a number of nonrandomized combined modality protocols which have utilized more "modern" chemotherapy regimens have been reported (table 13) (53a, 58,63,75,81,82,91,94,97,99,101-105). It is clear from these results that CR rates considerably higher than ever reported with chemotherapy alone have been seen. This, of course, is the first pre-requisite for superiority since cure requires a complete clinical regression of all demonstrable disease. The reported two year disease free survival rates demonstrate the same trend. In table 13 only two of these results represent true (as

TABLE 13.

RECENT RESULTS OF COMBINED MODALITY THERAPY OF SCLC

STUDY	DRUGS	RADIATION DOSE(r)	SCHEDULE	CR %	DISEASE FREE(%) 2YR	3YR	5YR
MDA (2)	CAV-VP	5000	LATE	80	47	32	--
MSK (1)	CAV/VP-P	5000	LATE/CONC	83	38	16	16
FRANCE	CAV-VP-P	5000	SPLIT	85	35	--	--
NCI (3)	CMCn/VAPr	4000	EARLY/CONC	78	42	37	18
ARIZONA	CAV-VP	4000	LATE/CONC	76	44	35	--
VANCOUVER	CAV/VP-P	3000	INITIAL/CONC	70	35	--	--
SECG (3)	CAV	4000	SPLIT	62	28	20	--
LONDON (2)	HiD-C	4000	LATE	56	30	18	--
NCOG	VP-AM/PrCnV	5000	LATE	49	26	14	--
SECG	CAD	4500	MID	50	20	--	--
TORONTO	VP-P	2500	LATE	64	15	--	--
TORONTO	CAV	2500	LATE	52	18	10	--
POG	CAV+/-VP	3000	MID	41	25	15	--
CALGB	MACCnV	4500	SPLIT	49	20	--	--
SWOG (1)	CAV	3000	MID	48	15	9	9

Chemotherapy: A=Adriamycin; C=cyclophosphamide; Cn=CCNU; D=DTIC; M=methotrexate; P=platinum; Pr=procarbazine; V=vincristine; VP=VP-16. x/y=alternating. RT schedule: Split=split course; Mid=after 1-2 cycles CT; Late=4-6 cycles CT; Conc=concurrent with CT (1)=True survival rates; (2)=With autologous bone marrow; (3)=Randomized trial.

opposed to actuarial) long term followup data. The MSK study, compared to a more traditional combined modality program, demonstrates an approximate doubling of the five year survival rate with the use of different radiation dosage and scheduling and more optimal chemotherapy (94,105). Obviously, the best means to come to grips with this question is through randomized studies. This would help settle the three most frequent criticisms of the uncontrolled trials, namely, whether increaed toxicity warrants such an approach; that the combined modality series were biased towards selection of a population of patients with a better prognosis because they were judged capable of undergoing more aggressive therapy; and that therefore no real long term benefit will ensue. To date, of several randomized studies, three have been reported in detail. The earliest study from London demonstrated no impact on local relapse rates or survival (106). The NCI study demonstrated an improved complete response rate and local control, and prolonged relapse free survival. At the time of reporting, overall survival was not statistically significantly different, but there were only 37 patients in each arm (97). The most recently reported study from SECG demonstrated an improved CR rate, a reduction in local failures and a slight but statistically significant improvement in survival in the irradiated group. In this study, after completion of induction chemotherapy and radiation therapy, patients who had not progressed were analyzed separately. An even greater advantage for the irradiated group in terms of two and three year survival was seen (102). At this time, it appears that CR is probably increased with combined modality treatment and this is most likely true for local control as well. The studies are not mature enough to assess the true impact on the primary question of long term survival benefit. In addition, it is probable that more efficacious chemotherapy regimens now exist than were employed in these randomized studies. It will be necessary to incorporate these into additional controlled trials. In terms of designing potentially optimal protocols, perusal of table 13 suggests certain trends. Higher doses of RT may be better, especially if lower doses are not given concurrently with chemotherapy. True non-cross-resistant chemotherapy combinations given in rapid alternating fashion seem to have had an impact. Interruption of chemotherapy early to give radiation appears to be sub-optimal. Radiation should probably be initiated early and concurrently with chemotherapy or be given later following several cycles of cytotoxic agents.

Enhanced toxicity is of critical concern when combining modalities. There is good evidence that this may be a major problem, but that protocol design is a definite determinate of these events. For example, in the NCI study, an extremely high incidence of severe and frequently fatal radiation pneumonitis occured in the irradiated group (107). These patients received RT concurrently with unusually high doses of cyclophosphamide as well as methotrexate, both known to be capable of producing pulmonary toxicity themselves, which suggests an additive effect. Similar experience has been reported by others (108). In contrast, with a different protocol in terms

of drugs and RT scheduling, the SECG study demonstrated no significant difference in any toxicity between the groups (102). Similar ability to curb very severe or fatal bone marrow, lung or esophageal toxicity by protocol design has been demonstrated in the non-randomized studies summarized in table 13.

A role for radiation therapy in ED has to date not been demonstrated. Because of the data derived from combined modality treatment of LD, it would seem reasonable to consider this modality in patients who have achieved a CR of metastiatic disease in an attempt to reduce their likelihood of local failure, which does occur in a substantial proportion of such patients (95).

THE ROLE OF SURGERY IN SMALL CELL LUNG CANCER

Typically, SCLC presents as a rather proximal lesion and bronchial and hilar lymph node metatases (N1) are quite common. Two-thirds of patients have clinical evidence of distant metastases at the time of diagnosis. Even in patients who do not appear to have systemic spread, autopsy studies done within 30 days of evaluation demonstrate that the majority have evidence of undectected metastases. Finally, in those patients who would be deemed operable by classical TNM staging criteria, 70% will have evidence of mediastinal lymph node involvement (N2), a situation which has traditionally been considered a sign of nonresectability. In the past two decades, these observations have led to a broadly accepted policy that surgical resection does not play a role in the treatment of SCLC. This opinion was reinforced by a study carried out by the British Medical Research Council. In that study, patients with a diagnosis of SCLC, who were deemed clinically operable, were randomized to attempted surgical resection or radiation therapy. The long-term followup data from that trial indicated that no persons randomized to surgery were alive at 5 years (90). However, two problems exist in the interpretation of that data. Entry criteria required that the patients must have had a bronchoscopic diagnosis of SCLC, thus all had proximal lesions. Secondly, the study was performed prior to the introduction of effective chemotherapy for this disease. Therefore they had no other significant treatment except subsequent radiotherapy. In recent years, a re-evaluation of this position has occured. The problem of high frequency of local-regional recurrence was noted earlier, being the primary first site of relapse in patients with LD treated by chemotherapy alone (table 12). Since this may, in part at least, be a problem of "bulky" disease and inadequate drug delivery, an additional modality for local "debulking" or eradication could be surgical. Also, all patients with SCLC do not neccessarily have proximal lesions or nodal metastases and this more localized subset might conceivably benefit from a different approach to their management. Some retrospective studies have lent credence to this concept. The VA Surgical Oncology Group studies from the 1960's and 1970's included prospective trials in patients with clinically operable lung cancer of all histologies who were randomized to no further treatment or single agent chemotherapy (regimens that would now be considered ineffective in SCLC). Their reviews identified 132 patients with SCLC entered into these

TABLE 14.

RESULTS OF SURGICAL THERAPY IN SMALL CELL LUNG CANCER

RETROSPECTIVE STUDIES

STUDY	STAGE	# PTS	M.S.(MOS)	SURV(%) 2YR	3YR	5YR	OTHER Rx PRE-OP	POST-OP
VASOG	ALL	132	--	34	27	23	0	(CT)
	I	65	--	52	46	40	0	(CT)
	I-No	26	--	55	51	43	0	(CT)
	II	39	--	18	9	9	0	(CT)
	III	28	--	18	8	4	0	(CT)
SEATTLE	ALL-S	85	--	51	38	27	?	VAR
	LOC-S	41	46	65	53	40	?	VAR
	REG-S	44	18	38	26	17	?	VAR
	LOC-NS	68	12	16	3	0	?	VAR
	REG-NS	285	10	10	3	3	?	VAR
SWOG	ALL-S	15	25	45	33	--	0	CT+RT
	ALL-NS	246	11	14	7	--	CT+RT	
DENMARK	ALL-S	24	--	--	--	18	0	CT+/-RT
	VLD-NS	55	--	--	--	5	CT+/-RT	
TORONTO	VLD NS	33	19	--	--	23	CT+RT	
	ALL LD	214	11	--	--	10	CT+RT	

PROSPECTIVE STUDIES

STUDY	STAGE	# PTS	M.S.(MOS)	SURV(%) 2YR	3YR	5YR	OTHER Rx PRE-OP	POST-OP
MAIN WG	ALL(I)	24	--	--	21	--	0	0
MAASEN	ALL	93	--	--	23	--	0	VAR
VANDERBILT	ALL	8	--	~50	--	--	CT	CT+RT
MDA	ALL	8	27+	~50	--	--	0	CT+RT
TORONTO	ALL	35	20	--	--	24	0/CT	RT,CT/O
SUNY	ALL	23	--	52	~44	--	0/CT	CT/O
MAIN	Is	--	--	--	21	--	0	0
MAASEN	Is	34	--	--	32	--	0	VAR
	No	25	--	--	40	--	0	VAR
CHICAGO	Ic	7	22+	28	--	--	0	CT+RT
VANDERBILT	Is	2	--	50	--	--	CT	CT
TORONTO	Is	20	19	40	40	40	0/CT	CT+/-RT
SUNY	Is	6	36+	--	83	--	0	CT
MAASEN	IIs	16	--	--	25	--	0	VAR
VANDERBILT	IIs	3	15+	67	--	--	CT	CT
TORONTO	IIs	9	18	*	*	*	0/CT	0/CT/RT
SUNY	IIs	5	--	60	~40	--	0	CT
MAASEN	IIIs	43	--	--	14	--	0	VAR
VANDERBILT	IIIs	3	<15	33	--	--	CT	CT
TORONTO	IIIs	6	20	*	*	*	CT	0/CT/RT
SUNY	IIIs	12	--	33	24	--	CT	0
*TORONTO	II+IIIs	15	19	52	40	20	0/CT	0/CT/RT
ECOG	I-IIIs	20	12/20 NED	MFU 21.5 mos			CT	CT

CT=Chemotherapy; RT=Radiotherapy; VAR=Treatment varied;
S=Resected; NS=Not resected; VLD=Resectable at diagnosis;
LD=Limited Disease; Is=Surgical Stage I; Ic=Clinical Stage I.

programs. Of note, a significant number of these patients survived for 2-5 years without further effective treatment. This was notably true for patients with stage I tumors, especially without nodal metastases in which 5 year survival exceeded 40%. Although not specifically stated, many or most of these patients may have had peripheral lung lesions. It is of interest, however, that even those patients with stage IIIMO disease had survivals not too unlike those seen with present day standard chemotherapy, although it should be kept in mind that even that group were clinically "operable" at diagnosis (109) (table 14). A different type of study was published from Seattle, where all patients with a diagnosis of SCLC in the community cancer registry were analyzed. 85 patients were identified who had surgery as their initial treatment modality. Again, very similar numbers are seen for long-term survivors, especially patients without regional lymph node metatases (40%) at five years). Although these patients were treated during the era of effective chemotherapy, the majority of the long-term survivors with local or local-regional (stage I and II) disease had received no further treatment (110). Again, it is probable that many of these patients had peripheral lung lesions as their tumor presentation. Retrospective analyses from SWOG and Denmark of SCLC patients who had undergone surgery as the initial part of their overall treatment indicated a favorable survival pattern (111,112). These kinds of observations led investigators from several centers to undertake prospective evaluation of the utility of surgical treatment as part of the management of some patients with SCLC (36-42, 114-118). Unfortunately, each of these studies were carried out with different design including selection of patients to be resected from the standpoint of stage, the timing of the surgery, the use of other modalities, and, if pre-surgical treatment was employed, the degree of response required to make a patient eligible for attempted resection of residual disease. Also, different post-operative management occured, ranging from almost none to aggressive chemotherapy and radiation. Table 14 summarizes these studies. It is clear that patients who were considered operable at diagnosis (stage I or II disease) had impressive survival results and these appear to be better than the retrospective studies if effective post opertive treatment was employed (39,40,116-118). There is also a suggestion that patients who presented with clinical stage II or III disease, and, after preoperative therapy, were then deemed operable had survival that might be considered superior to those seen with standard, non-surgical treatment. A more organized attempt to address this latter possibility has been undertaken by ECOG and is in progress. Patients with LD are given pre-operative therapy, and then those who are clinically operable and have had at least a partal response are randomized to surgery or continued non-surgical treatment. This trial is based on an earlier pilot study in which a potential impact of this type of approach was observed (37). One fact is clear from these studies. The frequency of local-regional relapse after surgical resection is very low, even better than that seen in patients whose thoracic disease has been managed by combined chemotherapy and radiotherapy (table 12). In terms of survival, however, a note of caution is advisable. The Toronto group retrospectively evaluated their experience with the treatment of 247 LD patients with combined modality therapy. They identified 33 who would have been

considered operable at diagnosis ("very limited disease"). Patients with peripheral nodules were excluded. Their local control and survival was superior to the other 214 patients. However, the 5 year survival of the "very limited disease" patients (23%) was almost identical to the results of their prospective surgical series (39,113). This suggests that patients with very limited disease may be a separate subset with an inherently better prognosis and should not be compared with all patients with LD SCLC, most of whom are stage III and never operable. This study also highlights the relatively few patients in whom this approach might even be applicable (perhaps 5-10% of all patients with SCLC and 15-25% of all patients with LD) (40,113,115).

In summary, it does appear that the few patients with SCLC who present with peripheral lesions, with or without bronchial or hilar lymph node metastases, and who have no evidence of mediastinal or distant spread, should be considered for primary surgical therapy and post-operative chemotherapy/radiotherapy. Parenthetically, many of these patients don't have a tissue diagnosis until the resection. For patients with stage IIIMO or proximal stage II lesions, the role of surgery is unsettled and should be considered investigative. The results of randomized studies where the patients are carefully stratified for extent of disease prior to surgery or no surgery will be required before this question can be more definitively answered.

THE PROBLEM OF CENTRAL NERVOUS SYSTEM METASTASES

SCLC manifests brain and other CNS metastases in a high proportion of patients, exceeding the frequency for most other malignancies. Several reports have documented that 4-27% of patients have evidence of brain metastases at presentation (95,119-122). A prospective evaluation utilizing routine CAT brain scans showed that 15% of patients had demonstrable brain metastases when first diagnosed. In 5% of these patients (1/3 of the total with brain metastases) no neuropsychiatric signs or symptoms were present. Of note, 16% of all patients who were otherwise free of clinical signs of other extrathoracic metastatic sites had brain involvement and 80% of these were asymptomatic (123). During the course of the disease, another 20-25% will develope clinical evidence of brain lesions and up to 60% have evidence of spread to this organ at autopsy (119-121). In a lesser, but significant, number of patients, recurrence (or presentation) of spread to the meninges or to extradural sites of the spinal cord are also seen. It is common for more than one of these sites to be involved in the same patient. As many as 80% of patients (including autopsy data) may have some form of CNS involvement during the course of their disease (51,121). Thus, CNS involvement produces a significant problem both in terms of morbidity, and also mortality. The frequency of CNS metastases has sharply risen as the length of survival in this disease has become prolonged. The cumulative hazard of developing CNS spread reaches 50% or greater by two years of survival (120,124,125). There is conflicting data as to whether there is a greater risk of such subsequent involvement in patients with ED versus LD at presentation (120,125). Nevertheless, all prognostic groups of patients are at major risk for this complication. Patients who develope brain metastases have a worse overall prognosis than patients without when corrected for

TABLE 15. Ref. 120,124

RESULTS OF PROPHYLACTIC BRAIN IRRADIATION IN PATIENTS WITH SCLC WHO ACHIEVE A COMPLETE REMISSION

INCIDENCE OF BRAIN METASTASES (%)

STUDY	#	PBI	NO PBI
NCI *	123	16	38
MARYLAND **	90	13	30

PRIMARY (FIRST SITE) BRAIN RELAPSE (%)

STUDY	#	PBI	NO PBI
NCI	123	0	17
MARYLAND	90	3	25
OTHERS	241	3	--

CUMULATIVE PROBABILITY OF BRAIN METASTASES (%)

STUDY	#	1 YEAR		2 YEARS	
		PBI	NO PBI	PBI	NO PBI
NCI	123	10	20	25	45
MARYLAND	90	8	32	24	45

ACTUARIAL SURVIVAL (%)

STUDY	#	1 YEAR		2 YEARS	
		PBI	NO PBI	PBI	NO PBI
NCI	123	38	27	27	12
MARYLAND	90	23	15	12	8

* 75 patients received PBI ** 30 patients received PBI

other factors of stage and sites of involvement (119,121). Some studies indicate that as many as two-thirds of patients who develope brain metastases may have an objective or symptomatic palliation of their problem (51), but nearly one-half will eventually succumb to this complication (126). Long term survival is rare. The CNS is a sanctuary site to chemotherapy, and to date, this modality has had no impact on this problem.

Historically, a major contribution to the curability of childhood acute lymphoblastic leukemia was made by the introduction of CNS prophylaxis. As is true of this disease, it is presumed that in many patients, the metastases exist in a microscopic form at the time of diagnosis. Because of the known radiosensitivity of SCLC, many investigators explored the potential of prophylactic brain irradiation (PBI) as part of the treatment program. Analysis of several non-randomized studies suggested that the overall incidence of brain relapse could be reduced from 22% to 8% by PBI (51,95). In particular, this reduced the cumulative risk of brain relapse significantly at all time points (120,124,125), and in one study, the survivorship at 30 months was significantly increased by 10-15% (120). Seven randomized studies were carried out and five of these showed a statistically significant reduction with the overall values being 20% for no PCI and 6% with irradiation (127). Median survivals were unaffected by this intervention. However, that would be predicted since the long-term survival rate is considerably lower than 50%. Unfortunately, none of the randomized studies were large enough or had sufficient followup to answer the more critical question of whether PBI contributes to an increase in the potential cure rate. Cure requires initially a CR of all apparent disease. Secondly, the vast majority of patients with long disease-free survivals present with LD. Thirdly, the subgroup most likely to be affected in terms of cure would be the LD patient, in CR, who has a brain relapse as the initial and sole site of recurrence. Only two published retrospective studies have attempted to address this specific setting. The NCI group found that there was no significant impact of PBI except in patients who had achieved a CR. Nearly 100% of patients who did not achieve a CR but survived 2 years developed CNS metastases irrespective of whether they did or did not receive PBI. Almost certainly many of these relapses represented seeding from the uncontrolled primary or other metastiatic sites (120). In terms of patients who achieved a CR, the NCI and University of Maryland studies demonstrated the following results: (a) the overall probability of developing brain metastases was reduced by PBI; (b) the cumulative probability of brain metastases was reduced at 1 and 2 years with PBI; (c) the frequency with which the brain was the first site of failure was significantly reduced in patients who received PBI. This compared favorably with the combined results of other studies (127); in addition, in the Maryland study, no patients in CR who received PBI had the brain as the sole site of relapse whereas 15% of the no PBI group had such an occurence; (d) the actuarial survival at 2 and 3 years was improved if PBI was given, but these values were not statistically significant, possibly due to the small number of such patients involved (table 15) (120,124). These data combined patients with

ED and LD. The NCI group attempted to assess their results in terms of LD patients alone and although there was a statistically significant reduction in brain relapse at 2 and 3 years in the PBI recipients, an impact on LD patients with CR could not be demonstrated in terms of site of first relapse or survival, possibly due to the numbers of subjects in each group. Therefore, though the trends suggest that PBI would have a survival impact on the subset of patients with LD in CR, this has yet to be proven. To demonstrate such an outcome, as was true for acute leukemia, will require higher percentages of long term survivors from the primary modalities and a large scale randomized trial. Recent uncontrolled combined modality trials which show a trend towards better survival outcomes (table 13) all utilized PBI. Only four of these studies addressed the question of first site of relapse in the brain of patients achieving a CR. 7 of 84 such patients (8%) had their first relapse in the brain, consistent with the predicted range of values (63,94,99,100). However, no similar study in which PBI was not given is available to assess the CNS relapse rate in aggressive protocols in the absence of that modality. If CNS relapse were to be reduced by only 50% in such patients, then a potential improvement in the cure rate might theoretically be appreciated if permanent control of other sites of disease is accomplished in even 25% of all LD patients. Nevertheless, at the present time, in the absence of more definitive data, it is recommended by most investigators that PBI be reserved for patients who achieve a CR. If given before 6 months of treatment, when the rapid increases in brain relapse occurs, it appears to be effective (51,127).

The question of major long term sequellae has been raised in some individual studies, including crippling dementia and other neurologic syndromes (51,125,127). Careful evaluation of such studies as well as others with lesser degrees of CNS complications suggest that certain chemotherapeutic agents given, as well as the total RT dose to the brain, are critical determinants of these problems. Recently, one sequential study has demonstrated that an RT dose for PBI of 2500 r was sufficient to produce the desired low levels of brain relapse yet no significant adverse sequellae were seen (128). In the NCI long-term followup study, careful neuropsychiatric and CAT scan evaluations were carried out on survivors. Subtle mental function and CAT scan abnormalities were seen in 80% of those who had received PBI. Yet only 1 of 11 patients who received PBI required functional assistance for impaired memory. It is of interest that only 3 patients who had not received PBI were long term survivors. One of these three had similar subtle abnormalities on their studies (5). Of the 17 long-term survivors in the SWOG followup, none had clear impairment of neurologic function. All had recieved PBI (6).

There is a significant incidence of other sites of CNS failure as well. This includes meningeal carcinomatosis, extradural cord compression and intramedullary lesions of the spinal cord (120,121,124,125,129,130). As with brain metastases, these complications are increasing in frequency as survival has been prolonged. The cumulative frequency of extracranial nervous system (ECNS) relapses in the Wisconsin series was 14% at one year and 22% at two years (125). This problem is not prevented by PBI

(120,124,125). When PBI was employed, the cumulative incidence of ECNS relapse was actually higher in patients receiving PBI and was twice that of brain relapses in the PBI treated patients. Based on these observations, they have begun a pilot program of prophylactic RT to the entire neuraxis.

In summary, CNS relapse is a major impediment to long-term disease free survival in SCLC and the role of radiation prophylaxis remains to be definitively demonstrated.

OTHER TREATMENT MODALITIES

Only a limited number of trials of alternative or additive modalities beyond chemotherapy, radiation and surgery have been published. Biological response modifiers (BMR) have occasionally been studied in SCLC. Non-specific immunostimulation with BCG or other agents has demonstrated no impact on response rates or survival (51). One study, employing a randomization schedule of the thymic hormone, thymosin, demonstrated an improved disease free survival in the hormone treated patients (131). No confirmatory studies have been published. As noted in the section on biology, SCLC cell lines are deficient in HLA expression and B2 microglobulin production. In vitro, this defect can be reversed by exposure of the cells to interferon (22). One published trial of interferon-alpha in patients with SCLC suggested that there was possibly a significant prolongation of time before disease progression in patients who were not receiving other therapy during the interval (132). A variety of trials employing alternate radiotherapy schemes such as whole or hemi-body irradiation or radiation of distant metastatic sites have not met with success (51,97). A randomized trial of chemotherapy plus warfarin, with the hypothesis of interfering with the establishment of mestastases, indicated a survival advantage in the group receiving warfarin. This has not been confirmed. (133).

FUNCTIONAL STATUS OF LONG TERM SURVIVORS

The quality of life of persons who have undergone these aggressive therapy protocols is a valid and necessary part of the evaluation of outcome. Few studies have carefully assessed these parameters. However, the data from MDA, NCI and SWOG represent an attempt to evaluate these parameters (5,6,8,). It seems clear from these reviews that the vast majority of long-term survivors are functioning at or near their pre-morbid level. Problems related to radiation toxicity of the lung, brain and esophagus exist and have been referred to in earlier sections. Nevertheless, these appear to be the minority and only very occasionally cause major deficits in patient function in the long term. Second malignancies, especially leukemia, have been observed in a rare patient (51). At present it would appear that the potential for long survival and cure in a proportion of properly selected patients justifies the risk of toxicity of aggressive treatment protocols.

NEW APPROACHES TO CANCER THERAPY

Preceding sections have referred to some of the approaches that are presently being explored at the clinical level including chemosensitivity testing, new chemotherapy agents, different schedules of chemotherapy administration, adjuvant radiotherapy to the thorax and CNS and surgical adjuvant therapy. Other areas of investigation which have much more theoretical but exciting potential are primarily at the laboratory and pre-clinical levels of development. These concepts apply to problems encountered in all types of malignant disease. They include such concepts as identifying mechanisms of drug resistance and attempting to bypass or modulate these processes; employing monoclonal antibody conjugates to deliver chmotherapy or radionuclides in a more targetted fashion; identification of essential growth factors and their receptors with the goal of interfering with cellular proliferation; and application of newer BMR technology. The reader is referred to some recent reviews of the status of some of this research (134-136).

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