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Chemotherapy of Small Cell Lung Cancer

Heine H. Hansen and Paul E.G. Kristjansen

INTRODUCTION

THE MANAGEMENT of patients with small cell lung cancer (SCLC) has undergone major changes during the past 20 years. Before 1970 surgery and radiotherapy were the most common forms of treatment, but these local methods provided only rarely effective long-term control, when used as single treatment modality. Appreciation of the frequency and extent of metastases coupled with the sensitivity of SCLC to a variety of chemotherapeutic agents have since then led to the present emphasis upon the central role of systemic chemotherapy. These changes have resulted in a 5 fold increase in median survival and a long-term disease-free survival of over three years duration in 5 to 10% of the group as a whole, and in 15 to 20% of patients presenting with limited disease extent and other favourable prognostic factors [1]. Even though considerable progress has been achieved, there is still no standardised treatment for SCLC. Work is being carried out in many centres and in national and international groups to obtain further knowledge of the special biological features of this disease entity, including the search for alternative treatments, with the hope that it will become a more readily curable disease.

PROGNOSTIC FACTORS

With the present available therapy it is important, before initiating therapy, to have its purpose in mind. In elderly patients palliation might be most important, while in other patients long-term survival or cure is the ultimate goal in spite of a more pronounced toxicity of the treatment. Accordingly it is important to evaluate the patients carefully with respect to the main prognostic factors before instituting treatment [2]. Some of the most important prognostic factors are listed in Table 1. The two key factors are pretreatment performance status and extent of disease. With respect to age and sex, patients below 60 years of age do better than those above 60 and females appear to have a better prognosis than males. In addition a pretreatment weight loss of more than 3 kg indicates a significantly worse prognosis.

The prognostic value of the histopathological subclassification of SCLC according to the WHO classification of 1982 is somewhat confusing, and there is disagreement regarding the prognostic impact of the various subtypes. This may reflect a lack of consistency of the different pathological findings rather than a genuine difference in the biology of the various subtypes. It is noteworthy that Carney *et al.* in 1981 observed an especially poor prognosis for patients with small cell carcinoma, characterised before treatment as tumours with small cell and large cell components [3].

These tumours always have been difficult to classify, which was one of the reasons for the recent proposal by the International Association for the Study of Lung Cancer for a new classification [4]. In this revised system, the tumours are categorised into three groups: (1) pure small cell carcinoma, (2) small cell/large cell, and (3) combined tumours with SCLC components. By this recommendation, which is simpler than the previous, the former inconsistencies are avoided, and the present prognostic knowledge is taken into account. With respect to the impact on survival of the anatomical stage, bone marrow metastases and CNS involvement *per se* result in a poor prognosis.

STAGING

The recognition of SCLC as a systemic disease has rendered the anatomical staging of patients as the basis of treatment outside an experimental setting less important. In order to assess prognosis and compare results from different trials, staging procedures are still important, although it is now evident that patients can be stratified into distinct prognostic groups on the basis of biochemical evaluation, including LDH, albumin and alkaline phosphatases, in combination with other descriptive data [2]. The anatomical stage is important for deciding whether to apply additional local treatment such as surgery and/or radiotherapy as part of the overall treatment plan. The tumour-node-metastases (TNM) system recommended by the Union International Contrele Cancer (UICC) has not traditionally been considered well suited for SCLC because more than 95% of the patients will be classified in the worst stage. The recent modification of the TNM system [5] has changed the situation. Two systems are now available for the staging of SCLC patients: (1) the classical Veterans' Association Lung Cancer Study Group (VALG) system of "limited" or "extensive" disease and (2) the recently revised TNM system. With regard to the VALG-system, the classification of patients with contralateral mediastinal or supraclavicular nodes and of patients with ipsilateral pleural effusions has not been uniformly handled by different investigators. A recent international workshop on SCLC [6] reached consensus on the following recommendation. The *limited* disease classification includes patients with disease restricted to one hemithorax with regional lymph-node metastases including hilar, ipsilateral and contralateral mediastinal and/or supraclavicular nodes. In addition patients with ipsilateral pleural

Table 1. Prognostic factors in small cell lung cancer

Stage, LD or ED	Subclassification†
Performance status	Bone metastases
Sex*	Liver metastases
Age	Blood biochemistry, especially LDH

*The prognostic impact of the patient's sex seems to have lessened along with the increase in incidence of SCLC in females (K. Østerlind, unpublished observation).
†Especially poor prognosis if large cell elements are observed.
LD = limited disease, ED = extensive disease, LDH = lactate dehydrogenase.

Correspondence to H. H. Hansen.
The authors are at the Finsen Institute, Department of Oncology, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.
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Table 2. Active agents in SCLC

Epipodophyllotoxins	Platinum derivatives
Etoposide	Cisplatin
Teniposide	Carboplatin
Alkylating agents	Others
Cyclophosphamide	Doxorubicin
Iphosphamide	Epirubicin
Nitrogen mustard	Lomustine
Hexamethylmelamine	Nimustine
	Carmustine
Vinca alkaloids	Methotrexate
Vincristine	
Vindesine	
Vinblastine	

effusion are included, independent of whether the cytology is positive or negative. The inclusion of the contralateral nodes in the mediastinum and the supraclavicular region was decided because the prognostic influence of these metastatic sites is less than that of distant metastases and also because the revised TNM system groups these patients in stage III and not in stage IV. The *extensive* disease classification includes all patients with disease sites not eligible for the limited stage, and this category is equivalent to stage IV. Stage I–III of the revised TNM then offers a subdivision of the limited disease category, which may be useful when local treatment modalities are evaluated.

CHEMOTHERAPY OF SCLC

The main treatment modality is chemotherapy, while the exact role of radiotherapy and surgery in combination with chemotherapy in the treatment of SCLC remains unclear.

The ideal therapeutic goal in SCLC is to reach the highest percentages of long-term disease-free survival (cures) with the lowest possible morbidity. We are still far from this ambition in spite of the fact that many antineoplastic agents have been shown to have antitumour activity in SCLC and to produce initial responses in up to 90% of the patients when given singly or in combination. For some time it has been considered evident that drug combinations with three or four drugs are superior to single agents, based on theoretical considerations as well as clinical investigations. Nevertheless recent results have suggested that epipodophyllotoxins either as single agents or in a two-drug combination with platinum might be effective as multi-drug combinations in producing initial responses [7].

The cytostatic treatment of SCLC is constantly subjected to changes and refinements. During the 1970s, the median survival was prolonged 4–5 times and possible cure was obtained in 5–10% of all patients. Major additional improvement has not been observed in the last decade, but a vast amount of studies has consolidated the early results. Many agents have exhibited antitumour activity and a list is shown in Table 2. The majority of studies include compounds such as etoposide, vincristine, cisplatin, cyclophosphamide, doxorubicin, lomustine and methotrexate. Among the most commonly used combinations are:

1. Cisplatin and etoposide
2. Vincristine, etoposide and cyclophosphamide
3. Cyclophosphamide, CCNU, vincristine, and etoposide
4. Cyclophosphamide, doxorubicin and vincristine.

Examples of these regimens including scheduling and the actual doses are given in Table 3. Etoposide has during the last few years increasingly been used in the initial treatment, since randomised studies have shown that combinations including this drug are superior to those without [8, 9].

When given aggressively, the regimens will result in a response rate in excess of 80% for both stages of SCLC. Complete response is produced in 30–40% of patients with limited disease and in 15–20% of patients with extensive disease.

A variety of options to improve treatment are under investigation. These include:

(a) Alternating "non-cross resistant" chemotherapy
(b) Scheduling of drug administration based on cell cycle analysis
(c) Anticoagulants in combination with chemotherapy
(d) Incorporation of new agents with high activity in the combination chemotherapy regimens
(e) Intensive high-dose chemotherapy with or without bone marrow support or transplantation
(f) Biological response modifiers.

Alternating vs. sequential chemotherapy

Background. Despite the initial chemosensitivity of SCLC, resistant clones present at time of diagnosis or emerging during therapy cause treatment failures in most patients. Evidence for a correlation between primary and emerging heterogeneity and clinical resistance has been derived from clinical investigations as well as from cell lines and human xenografts [10, 11]. A simple mathematical model based on a probabilistic nature of spontaneously arising resistant clones has been proposed by Goldie and Coldman [12]. Assuming exponential growth and a log kill at each dose of chemotherapy, the course of therapy with two truly non-cross resistant regimens, compared with sequential chemotherapy with the same regimens, was investigated by a computer simulation. Provided symmetry was present between the two regimens, i.e. same log kill and similar mutation rates producing resistance against each regimen, the alternating

Table 3. Commonly used regimens in SCLC

Combination	Dose (mg/m^2)	Route	Schedule
1. Cisplatin	80	I.V.	every 3 weeks, day 1
Etoposide	80	I.V.	daily on days 1–3 every 3 weeks
2. Cyclophosphamide	1000	I.V.	every 4 weeks, day 1
Lomustine	70	P.O.	every 4 weeks, day 1
Vincristine	1.3 (max 2.0 mg)		every four weeks, day 1 except first four weeks when administered weekly
Etoposide	70	P.O.	daily on days 2,3,4,5 every 4 weeks
3. Etoposide	50	I.V.	daily on days 1–5 every 3 weeks
Doxorubicin	45	I.V.	every 3 weeks
Cyclophosphamide	1000	I.V.	every 3 weeks
4. Cyclophosphamide	1500	I.V.	every 3 weeks
Doxorubicin	40	I.V.	every 3 weeks
Vincristine	2 mg	I.V.	every 3 weeks

I.V. = intravenously, P.O. = orally.

Table 4. Regimens and results in 6 controlled trials on sequential vs. alternating chemotherapy in small cell lung cancer

	Patients		Survival (mo)		CR	
Regimens	LD	ED	LD	ED	LD	ED
Stanford study, 1984 [15]						
S: CVLPz × 2 Irr CVLPz ... for 18 mo	28	56	10	7*	54%	20%†
A: EAM × 3 Irr CVLPz+EAM+CVLPz	28	50	16	10	42%	44%
Canadian studies, 1987 [16]						
S: CAV × 3 + EP × 3 (+Irr)	146	144	15.5	8.0†	45%	27%‡
A: CAV+EP × 3 (+Irr)	154	145	15.0	9.6	52%	39%
German study, 1987 [17]						
S: CAV × 8 + Irr	53	99	11.1	8.9‡	33%	15%
A: EVI+PAV × 3 + CML × 2 + Irr	51	99	13.4	9.9	52%	28%
Danish study, 1986–87 [18,19]	All patients		All patients		All patients	
S: CLVE ... +P/A/Vd/M/H for 19 mo	154	71	9.5	7.5‡	44%	21%
A_1: CLVM+EAV ... for 18 mo	151	66	11.5	7.5	37%	18%
A_2: CLVM+EAV+PVdH ... for 18 mo	152	66	12.0	8.0	41%	21%
American joint study, 1989 [20]						
S_1: EP × 4	–	344	–	9.5	–	17%
S_2: CAV × 6			–	9.8	–	12%
A: EP+CAV × 3			–	9.5	–	17%
ECOG study, 1990 [21]						
S: CAV × 6–8	–	294	–	10.6§	–	16%†
A: CAV+HEM × 3–4	–	283	–	11.5	–	23%

S = sequential, A = alternating, Irr = irradiation.
Agents: A = doxorubicin; C = cyclophosphamide; E = etoposide; H = hexamethylmelamine; I = iphosphamide; L = lomustine; M = methotrexate; P = cisplatin; Pz = procarbazine; V = vincristine; Vd = vindesine.
Significant differences between sequential and alternating regimens: *P = 0.001, †P = 0.03, ‡P = <0.05 and §P = <0.002 (after adjustment for prognostic factors).

principle resulted in a greater cure rate in the model. Fulfilment of the symmetry criteria cannot be proved in the clinical setting, and non-cross resistance has proved very difficult to ascertain.

Clinical experience. A review by Elliot *et al.* [13] concluded: (a) treatment schedules applying cyclic alternating non-cross-resistant drug combination in SCLC yield tumour responses comparable to those obtained with continuous regimens with a similar level of toxicity; (b) controlled trials have failed to demonstrate major advantages in terms of improved survival. Details of trial design, and especially the timing may be of critical importance; (c) further controlled studies are warranted. Careful attention to the trial design with elimination of confounding variables such as: radiotherapy, reevaluation of disease-free status and prolonged follow-up of larger number of patients will be necessary; (d) increased recognition of tumour cell heterogeneity as a major reason for treatment failure together with *in vitro* determination of drug sensitivity in cross-resistance may lead to a more rational future application of alternating chemotherapy.

A more recent updated review by Østerlind [14], did not change the conclusions of Elliot *et al.* In the 1984 review none of the trials published at that time were able to demonstrate a convincing advantage of alternating chemotherapy [13]. Results from six large controlled trials have been published since then [15–21] (Table 4). Schedules and regimens vary too much to make a meta-analysis feasible. The trials found small advantages of alternating chemotherapy for either limited stage [18, 19], extensive stage [15], or both stages [17], but no impressive differences. In addition to results shown in Table 4, the latest and one of the largest studies [21] found a 2-year survival of 10% in the alternating arm (CAV-HEM) vs. 4% in the sequential arm (CAV). It has been suggested [22, 23] that the etoposide-platinum (EP) combination, when given initially seem to be associated with a greater response rate than the CAV (cyclophosphamide, doxorubicin, vincristine) combination. This is likely to be a reflection of the fact that there is increasing evidence for an asymmetric cross-resistance between EP and CAV, since failures and non-responders on EP generally do worse after cross-over to CAV than do patients with EP as secondary treatment [24, 25]. Another explanation for the lack of realisation of the Goldie-Coldman predictions is a type II error problem of overlooking existing differences. The number of patients required in a two-armed trial, where the new treatment is supposed to result in a median survival of 18 months compared to 12 months in the control arm, is 448 patients (224 per arm) if the level of significance is the conventional 5% and the statistical power 0.75 [14]. Although the current clinical experience does not contradict or even weaken the Goldie-Coldman model, it is evident that alternating chemotherapy has not been a great step forward. The primary reason is probably the failure to fulfil the criteria of the theoretical model.

Scheduling of drugs based on cell kinetic observations. This has been the subject of a single clinical trial [8]. The superiority of etoposide scheduling based on data from flow cytometric DNA analyses was demonstrated.

Anticoagulants. The role of anticoagulants has been the subject of a small prospective randomised study by the VA Lung Cancer Study Group in the early 1980s [25]. 50 patients were randomised to receive chemotherapy and radiotherapy with or without warfarin. Median survival was 24 weeks for control patients and 50 weeks for the warfarin group. The difference related to warfarin was particularly evident in the subgroup of patients with disseminated disease at the time of randomisation and could not be explained by an imbalance of such prognostic factors as performance status, stage of disease, age and sex. The warfarin treated group also demonstrated a significant increase in time before progression suggesting an influence of warfarin treatment on the metastatic potential of the tumour. The use of warfarin in combination chemotherapy regimens has since been under large scale evaluation by several cooperative groups in the United States. A larger Cancer and Acute Leukemia Group B (CALGB) study on this topic [26] was published recently, comprising 328 patients, 294 evaluable, with extensive SCLC. Advantage was found in objective response rates for the warfarin treated group, while overall survival also was in favour of the warfarin group, but without reaching the conventional levels of significance. The use of warfarin should still remain experimental.

New drugs. The most active of the new drugs include carboplatin (JM-8) [27] and the podophyllotoxin derivatives, VP-16 (etoposide) and VM-26 (teniposide). The latter compound was recently shown to be highly active, with a response rate of 90% in untreated patients with SCLC [28]. The marked difference in response rates observed for the same compound (e.g. teniposide) in untreated (90%) and previously treated (18%) patients is important. This reveals that there are major methodological problems in the design and execution of clinical phase II trials with new agents in a highly chemosensitive tumour.

In the identification of active drugs selected for phase II trials, the importance of useful experimental models has been emphasised, although the correlation of drug activity between human cancer and animal and *in vitro* results is still poor [29]. It is important to note that newer active agents for years now have all been analogues of agents previously shown to be active in SCLC. A major breakthrough probably needs the introduction of agents with new mechanisms of action.

Special clinical situations

With respect to certain clinical situations in the management of SCLC, including CNS-metastases, superior vena cava syndrome and treatment at relapse, the recent literature has shed further light on the usefulness of chemotherapy. The palliation of symptoms, related to paraneoplastic syndromes, such as inappropriate antidiuretic hormone (ADH) syndrome still almost exclusively depends on the general responsiveness to the systemic therapy.

CNS metastases. The management of primary CNS-involvement at the start of systemic treatment is generally concomitant radiotherapy, since most cytostatic agents are presumed not to penetrate sufficiently into brain metastases. Recent observations have questioned this concept [30–33], since patients with CT-scan verified brain metastases from the start of treatment apparently do—at least initially—as well without as with irradiation, provided that chemotherapy is given initially. Complete responses on CT-scans of the brain and subsequent neurological alleviation after induction chemotherapy suggest, that initial brain metastases respond as frequently as metastatic SCLC tumours in other sites. The precise impact of these observations on the overall management awaits prospective analysis of large groups of patients. Also brain relapses have responded to chemotherapy with regimens containing etoposide or teniposide [34, 35]. Treatment of leptomeningeal carcinomatosis is generally disappointing. This may partially be due to the freqent occurrence of concurrent multiple metastases. The poor prognosis of these patients along with the lack of reliable objective parameters to monitor treatment outcome, makes the evaluation of various approaches difficult. Intrathecal methotrexate remains the most widely used treatment. The information on the use of other cytostatic agents is sparse. Intravenous high-dose etoposide therapy has been used with some effect but again with considerable systemic toxicity [36].

Superior vena caval obstruction. When superior vena cava syndrome is part of the initial presentation, radiotherapy was previously considered essential. Studies [37, 38] have shown that systemic chemotherapy alone in almost all cases produces sufficient relief from this condition, with the effect usually observed within a few days.

Treatment at relapse. Results of second line treatment with combination chemotherapy are generally disappointing, which in fact is a major problem, because most patients will relapse within a period of 10 to 12 months. The first recognisable clinical relapse may be situated either locally or in metastatic sites and subsequent treatment depends on this localisation. A multifocal relapse will usually lead to change of chemotherapy to include other active agents not used in the primary treatment. The response rates with such assumed non-cross resistant regimens are 20–25% with median duration of 3–4 months. Provided there was a chemotherapy-free interval before relapse, reinduction therapy with a combination that have produced response earlier in the course of treatment, seem to be considerably more efficient with response rates exceeding 50%, when retrospectively analysed [39, 40]. If the patient with relapse has not received etoposide + cisplatin earlier, this combination may also produce response rates of 50%.

Duration and intensity of treatment. There is a tendency to shorten the duration of therapy, provided that it is very intensive. A common policy is to re-evaluate patients at the end of the planned number of treatment cycles with careful restaging. This re-evaluation should include, at least, bronchoscopy and repetition of the initial staging procedures. If this examination indicates that the patient is in complete remission, treatment can be discontinued and the patient observed closely. About one third of patients *still* in complete remission one year after completing therapy will eventually relapse.

Accordingly, several studies have focused on the role of maintenance chemotherapy in prolonging time to relapse or even in avoiding relapse. Different trial designs are applied in these studies [7]. In some studies patients completing their induction chemotherapy received no further treatment, even at the time of disease progression in patients who had previously responded. These trials sometimes demonstrated a small survival advantage for the maintenance arm. Most trials have employed a reinduction chemotherapy at time of disease progression, either with the original regimen or with other combinations. In this group of trials there has been no survival benefit for maintenance chemotherapy. At present there is a consensus

Table 5. Intensification strategies

Multiple drug therapy
Consolidation
Alternating regimens
High dose chemotherapy
initial
late
Continuous chemotherapy

that 6 cycles of most active regimens constitute an acceptable standard [7].

The drug delivery can be intensified by increasing the doses or by reducing the intervals between treatments. The so-called intensive therapy covers several different approaches as listed in Table 5. In Table 6 five randomised studies testing effects of increased doses of drugs in the same combination are listed [41–45]. Dose escalation studies, supported by autologous bone marrow transfusion have yielded considerable toxicity, but so far no therapeutic advantage, neither when given as part of the initial treatment nor as late intensification therapy. A recent update on this matter [46] reviewed all available studies dealing with this issue. Most studies included only a very small number of patients and none were prospective randomised trials. Those intensification studies that included more than 25 patients are listed in Table 7 [47–49]. Preliminary reports on weekly chemotherapy suggest slight advantages but the follow-up is short and there are still no randomised comparisons.

TOXICITY OF CHEMOTHERAPY

As it is necessary to apply a maximal chemotherapy with or without irradiation a considerable level of treatment-induced complications should be anticipated. These include drug specific effects e.g. renal toxicity from platinum and neural toxicity from vinca alkaloids in addition to myelosuppression with serious infectious episodes during leukopenic episodes. The concept of improving the well-being of patients by means of parenteral hyperalimentation has failed to be confirmed in large randomised trials from several centres [50]. On the contrary the hyperalimentated patients did significantly worse regarding unpleasant complications such as sepsis, fluid overload, hyponatraemia, and hyperglycaemia, requiring insulin. Infection prophylaxis by use of co-trimoxazole allowed for higher dosages in outpatients in a recent investigation [42]. Overall results were not improved and side-effects were increased. It seems that myelosuppresion leads to serious problems in less than 25% and that lethal effects occur in less than 5% of patients in aggressive combination chemotherapy studies. Tardive side-effects have recently emerged in the increasing group of long term survivors. An increased tendency to develop secondary leukaemia, especially acute myelogenous leukaemia (AML), in SCLC patients treated with regimens including alkylating agents [51], has been recognised. Second primary tumours, including "non-small cell" lung cancers, should be looked for and histologically confirmed as they are potentially curable by surgery.

HAEMATOPOIETIC GROWTH FACTORS

Haematopoietic growth factors are glycoprotein hormones that regulate proliferation and differentiation of haematopoietic progenitors and the function of mature blood cells. Several substances have been applied in clinical studies: erythropoietin, granulocyte–macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), macrophage colony stimulating factor (M-CSF), and interleukin-3.

Clinical effects. G-CSF and GM-CSF are at present being tested in several clinical trials including with patients with SCLC. With regard to SCLC only one full study has been published [52]. Twelve patients with advanced SCLC were subjected to continuous infusion of G-CSF at the following dose levels: 1, 5, 10, 20 and 40 μg/kg/day for 5 days starting seven

Table 6. Randomised trials testing dosages of drugs in the same combination

Ref.		Regimen and dose (mg/m²)			Response					Statistical analysis of survival
					No.	Rate	CR	PR	MST	
Cohen		Lomustine	Methotrexate	Cyclophosphamide						
1977	I + II	100	15	1000	23	96%	7	15		NR
[41]	III	50	10	500	9	45%	–	4		
Figueredo		Doxorubicin	Vincristine	Cyclophosphamide						
1985	I	60	1	1500–2000	52	50%	11	15		NS
[42]	II	50	1	1000	51	39%	11	9		NS
O'Donnell		Cyclophosphamide	Vincristine	Methylomustine						
1985	I	2000	2	100	14	43%	3	3	43 wks	NS
[43]	II	750	2	75	14	71%	8	2	36 wks	
Wolff		Etoposide								
1986	I	100	(day 1–3)		26	4%	–	1	12.6 wks	
[44]	II	200			27	7%	–	2	20.0 wks	
	III	300			26	4%	–	1	22.5 wks	NS
Ihde		Etoposide	Cisplatin							
1987	I	80×5 days	27×5 days		21	86%	6	12	13 mo	
[45]	II	80×3 days	80×1 days		25	88%	8	14	11 mo	NS

PR = partial response, MST = mean survival time, NR = not reported, NS = not significant.

Table 7. Dose intensification studies with n > 25, testing megadoses as induction chemotherapy

	Regimens and dose	Stage	No.	CR	PR	MST	2 yr survival
Souhami 1985 [47]	Cyclophosphamide with/without etoposide 200mg/kg/4–600 mg/m² 2 courses	LD	26	50%	31%	38.6 wk	15% (DFS)
Thatcher 1985 [48]	Cyclophosphamide with etoposide 1.5–3.5g/m²/480 mg/m²	LD	111	56%	25%	11 mo	13%
Thatcher 1985 [49]	Cyclophosphamide with etoposide 2.5g/m²/480 mg/m²	LD	78	54%	25%	11 mo	

DFS = disease-free survival.

days before chemotherapy in a phase I study. In all 12 patients the number of peripheral neutrophils increased rapidly to a maximum of 100 × 10^9/l at 10 μg/kg/day. The neutrophils were shown to be functionally normal in tests of their mobility and bactericidal activity. The chemotherapy was a combination of doxorubicin, ifosfamide/mesna and etoposide. 9 out of 12 patients entered the phase II part of the study, and G-CSF was given to each patient for 14 days on alternate cycles of chemotherapy. The median duration of absolute neutropenia was reduced by 80% with a return to normal, or above normal, neutrophil counts within 2 weeks after day 1 of chemotherapy. Six severe infectious episodes were observed during the cycles of chemotherapy which did not include G-CSF, while no infectious episodes occurred when patients were treated with G-CSF. No toxicities resulted from the treatment. Recently, Crawford *et al.* [53] reported an interim analysis of a double-blind randomised trial of 126 out of a planned total of 240 patients with SCLC, who got recombinant human G-CSF (r-metHuG-CSF) as self-administrated subcutaneous bolus during chemotherapy with cyclophosphamide, doxorubicin and etoposide. The dose was 230 μg/m²/day on days 4–17 of a 21-day cycle, unless neutrophil count exceeded 10 × 10^9/l after day 12, in which case the r-metHuG-CSF was discontinued. Patients who developed febrile neutropenia during the first course of therapy were decoded and continued on open label CSF.

This open unilateral cross-over design makes a comparison of the treatment and placebo group beyond the first cycle very difficult especially with regard to the ultimate endpoints: response and survival. However, significant differences in duration of neutropenia and the incidence of neutropenic fever were demonstrable in favour of G-CSF. A new parameter, the "area over the curve" (AOC) was applied as an integrated measure of the severity of the neutropenia. AOC was defined in a semilogarithmic plot of absolute neutrophil count (ANC) against time as the area over the curve between the descending and the ascending intercept with a baseline ANC value of 0.5 × 10^9/l. Mild bone pain in 15% was the only observed toxicity related to r-metHuG-CSF.

A preliminary report [54] on a randomised comparison of cyclophosphamide, doxorubicin and etoposide plus/minus GM-CSF subcutaneously 10–20 μg/kg days 3–14 in 22 SCLC patients, described similar reductions in the myelosuppression but also cases of grade 3 to 4 toxicity due to GM-CSF.

CONCLUSION

Small cell lung cancer is a systemic disease and systemic chemotherapy forms the backbone of the overall therapeutic management. Many agents are active and several 2–4 drug combinations produce comparable results. Overall results have been unchanged for some years with complete or partial remissions being obtained in 80–90% of all patients with a median duration of 9–11 months. Median survival is dependent on the initial stage and other prognostic factors and is at present 11–16 months. In good prognosis subgroups, long-term survival and potential cure are obtained in about 20%, while the overall long-term survival does not exceed 10%. Elimination of resistant cells after initial response is the main obstacle in further improvement of the treatment. None of the newer approaches aimed at this seem to have improved the overall results significantly. New drugs with alternative mechanisms of action are needed, but critical reappraisals of known strategies may also be beneficial as we still have a lot to learn about the available tools in systemic therapy.

From the clinical data on CSF application published so far, it is reasonable to believe that CSF may serve to reduce treatment-related myelotoxicity. Whether this would reduce or only modify the overall morbidity is uncertain at present. Considering that myelosuppression seems to lead to serious problems in less than 25% and that lethal effects occur in less than 5% of patients in aggressive combination chemotherapy studies, reduced neutropenia is likely to decrease the incidence and severity of infections. A survival benefit obtained by avoiding reductions and delays of doses or by preparing the way for dose escalation or intensification of chemotherapy by e.g. shortening the interval between courses is possible and is presently being investigated in randomised trials.

In order to evaluate the potential usefulness of the CSFs, future studies should focus on clinically relevant endpoints such as survival and/or quality of life, depending on which basic assumptions are made. A survival benefit, achieved by an intensified therapy, made possible by CSF, would appear only if there really is a continuous dose-response relationship in SCLC, and only if no other toxicities are potentially dose-limiting. The palliative viewpoint assumes that myelosuppression is a major cause of morbidity that justifies prolonged prophylactic medication with CSF. Studies that follow this train of thought should compare CSF treatment with other means of prophylaxis such as oral antibiotics.

1. Hansen HH. Chemotherapy of small cell carcinoma: a review. *Q J Med* 1987, **63**, 275–282.
2. Østerlind K. Prognostic factors in small cell carcinoma. An analysis of 874 consecutive patients. In: Hansen HH, ed. *Lung Cancer: Basic and Clinical Aspects*. Boston, Martinus-Nijhoff, 1986, 129–152.
3. Carney DN, Matthews MJ, Ihde DC, *et al.* Influence of histological subtype of small cell carcinoma of the lung on clinical presentation, response to therapy and survival. *J Natl Cancer Inst* 1981, **65**, 1225–1229.
4. Hirsch FR, Matthews MJ, Aisner S, *et al.* Histopathologic classification of small cell lung cancer. *Cancer* 1988, **62**, 973–977.
5. Mountain CF. Staging of lung cancer: the new international system. *Lung Cancer* 1987, **3**, 4–11.
6. Stahel RA, Ginsberg R, Havemann K, *et al.* Staging and prognostic factors in small cell carcinoma of the lung. Consensus report. *Lung Cancer* 1989, **5**, 119–126.
7. Bunn PA, Cullen M, Fukuoka M. *et al.* Chemotherapy in small cell lung cancer: a consensus report. *Lung Cancer* 1989, **5**, 127–134.
8. Hirsch FR, Hansen HH, Hansen M, *et al.* The superiority of combination chemotherapy including etoposide based on *in vivo* cell cycle analysis in the treatment of extensive small cell lung cancer. *J Clin Oncol* 1987, **5**, 585–591.
9. Jackson DV, Zekan PJ, Caldwell RD, *et al.* VP-16-213 in combination chemotherapy with chest irradiation for small cell lung cancer: a randomised trial of the Piedmont Oncology Association. *J Clin Oncol* 1983, **2**, 1343–1351.
10. Vindeløv LL, Hansen, HH, Christensen IJ, *et al.* Clonal heterogeneity of small cell anaplastic carcinoma of the lung demonstrated by flow cytometric DNA analysis. *Cancer Res* 1980, **40**, 4295–4300.
11. Roed H, Vindeløv LL, Christensen IJ, Spamg-Thomsen M, Hansen HH. The cytotoxic activity of cisplatin, carboplatin and teniposide alone and combined determined on four human small cell lung cancer cell lines by the clonogenic assay. *Eur J Cancer Clin Oncol* 1988, **24**, 247–253.
12. Goldie JH, Coldman AJ, Gudauskas GA. Rationale for the use of alternating non-cross resistant chemotherapy. *Cancer Treat Rep* 1982, **66**, 439–449.
13. Elliot JA, Østerlind K, Hansen HH. Cyclic alternating "non cross resistant" chemotherapy in the management of small cell anaplastic carcinoma of the lung. *Cancer Treat Rev* 1984, **11**, 103–114.
14. Østerlind K. Alternating versus sequential chemotherapy in small cell lung cancer. *Lung Cancer* 1989, **5**, 173–177.
15. Daniels JR, Chak LY, Sikic Bl, *et al.* Chemotherapy of small cell carcinoma of the lung: a randomized comparison of alternating and sequential combination chemotherapy programs. *J Clin Oncol* 1984, **2**, 1192–1199.
16. Feld R, Evans WK, Coy P, *et al.* Canadian multicenter randomised trial comparing sequential and alternating administration of two non-cross resistant chemotherapy combinations in patients with limited small cell carcinoma of the lung. *J Clin Oncol* 1987, **5**, 1401–1409.
17. Havemann K, Wolf M, Holl R, *et al.* Alternating versus sequential chemotherapy in small cell lung cancer. A randomized German multicebnter trial. *Cancer* 1987, **59**, 1072–1082.
18. Østerlind K, Pedersen AG, Vindeløv LL, *et al.* Alternating or continuous chemotherapy of extensive stage small cell lung cancer. Results of a controlled trial on 204 patients. *Lung Cancer* 1986, **2**, 127–128.
19. Pedersen AG, Østerlind K, Vindeløv LL, *et al.* Alternating or continuous chemotherapy of small cell lung cancer. A three armed randomized trial. *Proc Amer Soc Clin Oncol* 1987, **6**, 195.
20. Roth BJ, Johnson DH, Greco FA, *et al.* A phase III trial of etoposide and cisplatin versus cyclophosphamide, doxorubicin, and vincristine versus alternation of the two therapies for patients with extensive small cell lung cancer: preliminary results. *Proc Amer Soc Clin Oncol* 1989, **8**, 225.
21. Ettinger DS, Finkelstein DM, Abeloff MD, Ruckdeschel JC, Aisner JC, Eggleston JC. A randomized comparison of standard chemotherapy versus alternating chemotherapy and maintenance versus no maintenance therapy for extensive-stage small cell lung cancer: a phase III study of the Eastern Cooperative Oncology Group. *J Clin Oncol* 1990, **8**, 230–240.
22. Fukuoka M, Furuse K, Saijo N, *et al.* A randomized study in the treatment of small cell lung cancer: cyclophosphamide, adriamycin and vincristine vs cisplatin and etoposide vs cyclophosphamide, adriamycin and vincristin alternating with cisplating and etoposide. *Lung Cancer* 1988, **4**, (Suppl.), A101.
23. Batist G., Carney DN, Cowan KH, *et al.* Etoposide and cisplatin in previously treated small-cell lung cancer: clinical trial and in vitro correlates. *J Clin Oncol* 1986, **4**, 982–986.
24. Evans WK, Osoba D, Feld R, *et al.* Etoposide and cisplatin: an effective treatment for relapse in small cell lung cancer. *J Clin Oncol* 1985, **3**, 65–71.
25. Zacharaski LR, Henderson WG, Rickles FR, *et al.* Effect of warfarin in small cell carcinoma of the lung. *JAMA* 1981, **245**, 831–835.
26. Chahinian AP, Propert KJ, Ware JH, *et al.* A randomized trial of anticoagulation with warfarin and of alternating chemotherapy in extensive small cell lung cancer by the Cancer and Leukemia Group B. *J Clin Oncol* 1990, **7**, 993.
27. Smith IE, Harland SJ, Robinson BA, *et al.* A very active new cisplatinum analogue in the treatment of small cell lung cancer. *Cancer Treat Rep* 1985, **69**, 43–46.
28. Bork E, Hansen M, Dombernowsky P, *et al.* Teniposide (VM-26). An overlooked highly active agent in small cell lung cancer. Results of a phase II trial in untreated patients. *J Clin Oncol* 1986, **4**, 524–528.
29. Roed H, Vindeløv LL, Spang-Thomsen M, Engelholm SÅ. Limitations and potentials of *in vitro* sensitivity testing of human small cell carcinoma of the lung. In: Hansen HH, ed. *Lung Cancer III*, Martinus Nijhoff, Boston. 1986, 77-89.
30. Kristjansen PEG, Hansen HH. Brain metastases from small cell lung cancer treated with combination chemotherapy. *Eur J Cancer Clin Oncol* 1988, **24**, 545–549.
31. Kantharjian H, Farha PAM, Spitzer G, *et al.* Systemic combination chemotherapy as primary treatment of brain metastases from lung cancer. *South Med J* 1984, **77**, 426–429.
32. Lee JS, Murphy WK, Glisson BS, *et al.* Primary chemotherapy of brain metastases in small cell lung cancer. *J Clin Oncol* 1989, **7**, 916–920.
33. Twelves CJ, Souhami RL, Harper PG, *et al.* The reponse of cerebral metastases in small cell lung cancer to systemic chemotherapy. *Br J Cancer* 1990, **61**, 147–150.
34. Postmus PE, Holthuis JJM, Haaxma-Reiche H, *et al.* High dose etoposide for brain metastases of small cell lung cancer. A phase II study *Br J Cancer* 1989, **59**, 254–256.
35. Giaccone G, Donadio M, Bonardi GM, Testore F, Calciati A. Teniposide (VM-26): an effective treatment for brain metastases of small cell carcinoma of the lung. *Eur J Cancer Clin Oncol* 1988, **24**, 1905–1906.
36. Postmus P, Haaxma-Reiche H, Berendsen HH, Sleifer DTh. High-dose etoposide for meningeal carcinomatosis in patients with small cell lung cancer. *Eur J Cancer Clin Oncol* 1989, **25**, 377–378.
37. Dombernowsky P, Hansen HH. Combination chemotherapy in the management of superior vena caval obstruction in small cell anaplastic carcinoma of the lung. *Acta Med Scand* 1978, **204**, 513–516.
38. Kane RC, Cohen MH, Broder LE, Bull MJ. Superior vena cava obstruction due to small cell anaplastic carcinoma. *JAMA* 1976, **235**, 1717.
39. Giaccone G. Second line chemotherapy in SCLC. *Lung Cancer* 1989, **5**, 207–213.
40. Andersen M, Kristjansen PEG, Hansen HH. Second line chemotherapy in small cell lung cancer. *Cancer Treat Rep* (in press).
41. Cohen MH, Creaven PJ, Fossieck BE, *et al.* Intensive chemotherapy of small cell bronchogenic carcinoma. *Cancer Treat Rep* 1977, **61**, 349–354.
42. Figueredo AT, Hryniuk WM, Strautmanis I, Frank G, Rendell S. Cotrixamole prophylaxis during high-dose chemotherapy of small cell lung cancer. *J Clin Oncol* 1985, **3**, 54–64.
43. O'Donnell MR, Ruckdeschel JC, Baxter D, McKneally MF, Caradonna R, Horton J. Intensive induction chemotherapy for small cell anaplastic carcinoma of the lung. *Cancer Treat Rep* 1985, **69**, 571–575.
44. Wolff SN, Birch R, Sama P, Greco FA. Randomized dose-response evaluation of etoposide in small cell carcinoma of the lung: a Southeastern Cancer Study Group Trials. *Cancer Treat Rep* 1986, **70**, 583–587.
45. Ihde DC, Johnson BE, Mulshine JL, *et al.* Randomized trial of high dose versus standard dose etoposide and cisplatin in extensive disease stage small cell lung cancer (abstr.). *Proc ASCO* 1987, 71.

46. Klastersky JA, Sculier J-P. Intensive chemotherapy of small cell lung cancer. *Lung Cancer* 1989, 5, 196–206.
47. Souhami RL, Harper PG, Linch D, *et al.* High-dose cyclophosphamide in small cell carcinoma of the lung. *J Clin Oncol* 1983, 3, 958–963.
48. Thatcher N, James RD, Steward WP, *et al.* Three months treatment with cyclophosphamide, VP-16 followed by methotrexate and thoracic radiotherapy for small cell lung cancer. *Cancer* 1985, **56**, 1332–1336.
49. Thatcher N, Stout DR, Smith DB, *et al.* Three months treatment with chemotherapy and radiotherapy for small cell lung cancer. *Br J Cancer* 1985, **52**, 327–332.
50. Weiner RS, Kramer BS, Clamon GH, *et al.* Efects of hyperalimentation during treatment in patients with small cell lung cancer. *J Clin Oncol* 1985, **3**, 949–957.
51. Pedersen-Bjergaard J, Østerlind K, Hansen M, *et al.* Acute non-lymphocytic leukemia, preleukemia, and solid tumors following intensive chemotherapy of small cell carcinoma of the lung. *Blood* 1985, **66**, 1393–1897.
52. Bronchud MH, Scarffe JH, Thatcher N, *et al.* Phase I/II study of recombinant human granulocyte colony-stimulating factor in patients receiving intensive chemotherapy for small cell lung cancer. *Br J Cancer* 1987, **56**, 809–813.
53. Crawford J, Ozer H, Johnson D and the G-CSF study group: Granulocyte colony stimulating factor: prevention of chemotherapy induced febrile neutropenia in patients with small cell lung cancer. A randomized double blind placebo controlled trial. *Proc ASCO* 1990, 884.
54. Schiller JH, Storer B, Oken MM, *et al.* Randomized trial of granulocyte macrophage colony stimulating factor in patients with small cell carcinoma of the lung. *Proc ASCO* 1990, 943.

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Head and Neck Cancer: Prognostic Factors for Response to Chemotherapy

M. Clavel and A.R. Maged Mansour

INTRODUCTION

CHEMOTHERAPY FOR cancer of the head and neck is now a major therapy alongside surgery and radiotherapy. Chemotherapy is important in all head and neck tumours whatever the histological type: squamous cell carcinoma, undifferentiated carcinoma of nasopharynx, or lymphoma. Tumours of the salivary gland and adenoid cystic carcinomas are uncommon diseases, but may eventually be treated by chemotherapy as well.

SQUAMOUS CELL CARCINOMA OF HEAD AND NECK

Patients with advanced head and neck squamous cell carcinoma have a very poor prognosis with a five-year survival of less than 30%. Most of the patients die from local disease due to recurrence, while some 6–7% develop metastases [1]. More than 20% of the patients develop a second primary, usually in the pharynx, larynx, bronchus or oesophagus. The rate of second malignancy is clearly related to the behaviour of the patients. With reductions in the intake of tobacco and alcohol, the rate declines.

In this review, we will consider chemotherapy for recurrent and metastatic disease, chemotherapy as part of a combined strategy for previously untreated advanced disease and second malignancy chemoprevention. Because the response to up-front chemotherapy is of major importance, the prognostic factors for response are crucial.

CHEMOTHERAPY FOR RECURRENT AND METASTATIC SQUAMOUS CARCINOMA

Monochemotherapy. Methotrexate (MTX), cisplatin (C), bleomycin (BLM) 5-fluorouracil (5-FU) and vincristine (VCR) are the most active drugs [2]. New drugs have some activity and include vindesine (VDS) and hydroxyurea (HU). Comparative studies have examined a potential dose-response effect for methotrexate, but so far methotrexate in the form of 40 mg/m^2 weekly is the well accepted standard monochemotherapy. New analogues such as 10-edam have similar activity.

Polychemotherapy. Many combinations have been evaluated in this subset of patients. Response rate with polychemotherapy is about 50% including a clinical complete response of about 10% [3]. Several authors reported a response rate higher with polychemotherapy than with monochemotherapy. Cisplatin-containing polychemotherapy is more active than non-cisplatin-containing regimens [4]. 5-FU was found to potentiate the activity of cisplatin *in vitro* and cisplatin/5-FU was demonstrated to be a safe and active manageable combination [5]. The EORTC have conducted a three arms randomised study comparing CABO (cisplatin, methotrexate, bleomycin, vincristine), CF and cisplatin alone. Both combinations were more active than cisplatin alone whilst no difference was found between CABO and CF.

The duration of response is still disappointing with a median of 4–6 months, whichever chemotherapy combination is used. Among many prognostic parameters, only performance status is associated with a high response rate to chemotherapy. Previously untreated patients fare significantly better than previously treated patients (surgery with or without radiotherapy). A high response rate, a short duration of response and a better activity in previously untreated patients are the rationale for a combined strategy including CT at an earlier stage.

COMBINED TREATMENT—CHEMOTHERAPY AND LOCOREGIONAL TREATMENT

Chemotherapy is now included in most of the therapeutic strategies for locally advanced squamous cell carcinoma, T3 and T4.

Correspondence to M. Clavel.
The authors are at the Centre Leon, 29 rue Laennec, 69373, Lyon Cedex 08, France.
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