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Chemotherapy of small cell lung cancer

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Despite the fact that small cell lung cancer (SCLC) is a very chemosensitive disease, the long-term results from the present treatment are very disappointing with 5 year survival of less than 5%. The present article is an overview of the chemotherapy used today and future treatment perspectives.
Most centers today use a combination of epipodophyllotoxin derivates (Etoposid, (VP-16) or Vumon (VM-26) and a platin derivate (Cisplatin or Carboplatin) as a "standard" treatment for SCLC. Less toxic treatment for the elderly patients are described, especially the role of oral single agent treatment.
"High dose" treatment with or without bone marrow support has not yet resulted in prolonged survival. Future treatment strategies are discussed.

Key words: lung neoplasms – drug therapy; carcinoma, small cell; brain metastases

Introduction

Lung cancer is one of the most important public health problems in the world. The incidence of this malignant disease continues to increase in the developed world, particulaly among women. By the year 2000 the estimated number of new cases worldwide is expected to exceed 2 million.[1] Approximately 25 % of all lung cancer cases are of the small cell variety (SCLC). Despite few or no symptoms about 60 % of the patients have documented distant metastatic disease at presentation.[2]

In contrast to the other major types of lung cancer, SCLC is highly sensitive to both chemotherapy and radiation therapy. However, patients with extensive stage disease are rarely cured, even with aggressive treatment. On the other hand patients with limited stage disease sometimes experience long-term progression free survival with chemotherapy with or without thoracic radiotherapy and, occasionally, cure. Furthermore, chemotherapy is effective in ameliorating the symptoms of the superior vena cava syndrome, bronchial obstruction, pleural effusion and even brain metastases. Virtually, all patients with SCLC should therefore receive chemotherapy as part of their initial treatment.

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"Standard" chemotherapy

A number of drugs have been identified with single agent activity in SCLC.[3] The relative effectiveness of the individual drug is difficult to compare because only few of them are studied in previously untreated patients, but mostly in heavily pretreated patients. However, most of the drugs have reported response rates of 30–60 % as single agent treatment (Table 1). Early randomized trials demonstrated that **combination chemotherapy** was superior to single agent treatment.[4,5] In the late 1970s and early 1980s cyclo-phosphamide-based combination chemotherapy regimens represented the most commonly used induction therapy. A typical example is the CAV regimen: cyclophosphamide/doxorubicin (adriamycin^{R})/vincristine which has demonstrated overall response rates of 65-90 % in limited stage disease and complete response rates of 20–40 % with a small number of 5 years survivors.[2,6]

Table 1. Active single agents in small cell lung cancer.

Drug	Approximate response rate (%)
Etoposide	75
Teniposide	75
Ifosfamide	60
Cisplatin	50
Carboplatin	40
Cyclophosphamide	40
Vincristine	35
Methotrexate	35
Doxorubicin	30
Hexamethylmelamine	30
Vinblastine	30
Vindesine	30
Lomustine	15

During the early to mid 1980s many clinical trials focused on the integration of etoposide into existing chemotherapy regimens. Although none of these trials yielded a major improvement in survival most were associated with a modest improvement in median survival which in some instances was statistically significant.[7, 8]

The combination of etoposide (E) and cis-platin (P) is of special interest because it appears to have the best therapeutic index of any regimens, and in a number of trials this combination (EP) has been used as the initial chemotherapy for patients with SCLC. Overall results in previous untreated patients show that the complete response rate average more than 50 % with a median duration of survival in these studies that compared favorably with results achieved with traditional induction regimens such as CAV or CAE (cyclophosphamide, doxorubicin, etoposide).[6–10]

While most of the treatment regimens today include cisplatin and etoposide, more recently cisplatin has been replaced by carboplatin in combination with oral etoposide in the treatment of poor prognosis patients with SCLC[11] and those studies suggested that the combination of carboplatin with oral etoposide is a highly effective regimen for the treatment of SCLC patients with results equal to and comparable with more intensive schedules.[11, 12] However, it is too early yet to evaluate the long term results (> 3 years) on that regiment. The median survival from the study by Carney[11] is 43 weeks (range 4–128). In one randomized study cis-platin was compared to carboplatin, both in combination with etoposide, and no difference was obtained with regard to response and survival.[12] The ease of administration of the combination of carboplatin and etoposide with acceptable toxicity would suggest that this combination could be the treatment of choice at least for a subset of patients with SCLC, especially those patients who cannot tollerate more intensively given treatment.

The strategy **of alternating "non-cross resistant" chemotherapy** was prompted by theoretical considerations put forth in a mathematical model developed by Goldie and Goldman.[13]

A study by Evans et al in 1987[14] demonstrating a better survival with a regimen of CAV in alternation with EP compared to CAV alone raised the clinical interest for this question in patients with SCLC. However, the possibility could not be eliminated, that the superiority of the alternating treatment was due to a better efficacy of the EP treatment than the CAV treatment. Two subsequent randomzied studies by Roth et al[9] and Fakuoka et al[6] compared CAV, EP and CAV alternating with EP, and no difference in survival was seen among the three treatment groups in either of the studies. The value of the sequential administration of two cycles of etoposide and cisplatin after completion of six cycles of CAV was evaluated in a large study of limited disease patients by Einhorn et al,[15] and the median survival was prolonged by seven months with etoposide and cisplatin.

However, the majority of studies using alternating non-cross resistant combination chemotherapy have not shown a major benefit for this approach.[16] Although alternating regimens produce only minimal survival advantages at best, they do reduce toxicity that depends on the cumulative dose of a single drug such as doxorubicin induced cardiomyopathy and cisplatin induced neuropathy. The problem is, however, that from a experimental therapeutic point of view the so called "non-cross resistant" treatment with CAV and EP are today not considered as a true non-cross resistant combination chemotherapy.[17]

The Copenhagen experience[18]

In Copenhagen clinical studies focusing on the treatment of patients with SCLC have been performed by the Copenhagen Lung Cancer Group since 1973. In the period 1985-1990 484 previously untreated patients ≤ 70 years old were included in study designed with the following aims: 1. to compare two induction regimens containing teniposide (VM 26), vincristine (VCR) and either cis-platin (P1) or carboplatin (JM-8) followed by an alternating chemotherapy and 2. to compare these regimens with alternating regimen alone.

Arm 1: D_1-D_1-D_1 evaluate – A-B-C-D_1-A-B-C-D_1 – evaluate

Arm 2: D_2-D_2-D_2- evaluate – A-B-C-D_2-A-B-C-D_2 – evaluate

Arm 3: A-B-C – evaluate – A-B-C-A-B-C-A-B – evaluate

A: Doxorubicine, VCR

C: Pl, hexamethylmelamine, vindesine

D_1: Pl, VM 26, VCR

D_2: JM-8, VM 26, VCR

There was no survival difference in patients treated with the two platinum containing induction arms, while the survival was superior in the two induction arms compared to the alternating control arm (Table 2).

Table 2. Median survival (M.s.) and 2-years survival.

	LD		ED		All	
	M.s. weeks	2 years	M.s. weeks	2 years	M.s. weeks	2 years
Reg. I	58	20 %	36	10 %	48	18 %
Reg. II	61	18 %	38	13 %	49	15 %
Reg. III	48	15 %	30	5 %	42	10 %

Treatment of elderly patients with SCLC

Approximately 25–30 % of newly diagnosed patients with SCLC are older than 65, and the number of elderly patients with SCLC will continue to increase over the next 20 years. It is therefore important to give greater consideration to the management of elderly SCLC patients. Single-agent chemotherapy have demonstrated to be very useful in the elderly patients. Etoposide or its analogue teniposide (VM-26) alone has yielded response rates of 65 to 80 percent in elderly patients, including complete responses in 20 to 25 percent of patients, only moderate toxicity and median survival of 9 to 11 months in controlled[19] and uncontrolled trials.[20] Although better results might have been obtained with combinations of drugs with or without radiotherapy no randomized trials have addressed these questions in this subgroup of patients. However, more recently it is reported that the combination of orally given etoposide in combination with carboplatin is a well tollerated combination also for elderly patients.[21]

Etoposide has clearly demonstrated schedule dependence. A study of Slevin et al[22] has shown that prolonged administration of etoposide produces greater responses than the same total dose given in a shorter time frame. Furthermore the study has demonstrated that the overall response rate and survival were significantly greater for patients who received 5 days of i.v. therapy than for those who received a single day of treatment. Randomized trial comparing intermittent and continuous etoposide in elderly patients with previously untreated SCLC are presently ongoing in Copenhagen.

Many factors may influence the approach to the administration of chemotherapy to the elderly patients. Co-morbid illnesses and/or performance status rather than the age are the principle factors which will dictate the therapeutic approach and for many of these patients the aim of treatment is to balance the probability of cure or palliation against the risk of toxicity and quality of life. The presence or absence of co-morbid disease leading to impairment of cardiac, pulmonary or renal function should be considered as well as other medication, which may lead to potential drug interactions with the chemotherapy. Furthermore, elderly patients have often poor compliance and errors in self-medication.

At present, single agent chemotherapy with oral etoposide seems to be an appropriate option for elderly patients with SCLC in whom the likelyhood of severe toxicity from combination therapy is high. The treatment is well tollerated and has shown to give a high response rate (75–80 %), and long term survivors (> 2 years) are reported even in this group of patients.[19] The most optimal schedule is not established and future studies should also include a comparisson of single agent treatment with "mild" combination treatment.

Dose intensity without bone marrow support

Drug delivery can be intensified by increasing the doses or by reducing the intervals between treatments. Intensification strategies include high-dose induction chemotherapy, late intensification chemotherapy with or without bone marrow support and weekly chemotherapy have been studies.

During the 70s and early 80s the clinical investigations hypothesized that a dose response relationship existed in the treatment of SCLC and "more chemotherapy was better", and early trials appeared to support these results.[23, 24] However, randomized trials comparing "high dose" regimens to "stand-

ard" doses failed to demonstrate significant differences in survival.[25–28] Retrospectively, however, it can be discussed whether the "high-dose" treatment really could be considered as such from an up-to-date point of view.

In a study by Ihde and co-workers[29] they failed to demonstrate a survival benefit in patients with extensive stage SCLC randomized to high dose therapy compared to standard dose therapy. They randomized 90 patients to standard dose PE vs. high dose PE. Patients randomized to the standard dose arm received 80 mg/m^2 of cisplatin days 1,3 plus 80 mg/m^2 etoposide days 1–3 for cycles 1 and 2. Patients randomized to the high dose arm received 27 mg/m of cisplatin days 1–5 and 80 mg/m^2 of etoposide days 1–5 for cycles 1 and 2. All patients received standard dose PE cycle 3 and 4. In cycles 5 through 8 completely responding patients continued standard dose PE, all other patients received either cyclophosphamide, doxorubicin and vincristine or if possible a combination drug program based on in-vitro drug testing of tumor cell lines established from individual patients. Despite 68 % higher doses and a 46 % higher dose-rate intensity actually given to patients randomized to high-dose PE compared to those randomized to receive standard dose PE, complete response rates (23 % vs. 22 %) and median survival durations (10.7 months and 11.4 months) respectively, were not statistically significant. Furthermore, dose escalation of chemotherapy was associated with enhanced toxicity.

Another approach to increase the total dose delivery was to evaluate the use of prolonged administration of chemotherapy, the so called **"maintenance therapy"**. Randomized clinical trials evaluating the maintenance chemotherapy for 5 to 7 months following 6 months of induction chemotherapy demonstrated that, although, the duration of initial treatment remission could be prolonged, survival was not significantly improved by this approach, and the treatment was associated with increased toxicities due to the protracted exposure to chemotherapy.[30–34]

Yet, another method for increasing the intensity of chemotherapy in SCLC is to intensify the schedule. Studies evaluating cisplatin, vincristine, doxorubicin and etoposide (CODE) have shown high response rates (> 90 %) and encouraging two year survival rates in patients with extensive stage disease. Once again, however, these results have not been confirmed in a randomized study evaluating four drug, high dose weekly chemotherapy against "standard" alternating CAV/PE.[35]

In contrast to "late intensification" Arriagada et al[36] reported recently a study of **"initial intensification"** randomized 105 patients to receive a first course of either "high dose" cyclophosphamide (300 mg/m^2) days 2–5 plus cisplatin, 100 mg/m^2 day 2 or "lower dose" of cyclophosphamide (225 mg/m^2) days 2–5 plus 80 mg/m^2 cisplatin on day 2. All patients received the lower doses of cyclophosphamide and cisplatin, plus doxorubicin and etoposide for course 2 through 6. Thoracic radiation was given concurrently in both groups starting with the second cycle of chemotherapy. Although there was no significant difference in complete response rate, the two year survival for the 55 patients who received the higher doses of chemotherapy was 43 % compared with 26 % for the 50 patients who were randomized to receive the lower doses of cyclophosphamide and cisplatin for cycle 1 ($p = 0.02$). One possible reason for their positive results was that the delivery of higher initial doses of drugs early prevented the emergence of chemoresistant tumor clones. They suggest that the advantage of only a 20 % to 25 % increase in the doses of cyclophosphamide and cisplatin may have been that the resultant toxicity was not severe, and did not necessitate delay of subsequent cycles of standard doses of chemotherapy as may have been the case in other trials which evaluated the use of much higher doses of drugs in cycle 1.

A meta-analysis of dose-intensity in SCLC involving 60 published studies failed to demonstrate a correlation between dose intensity of CAV (cyclophosphamide, adriamycin, vincristine) or cisplatin/etoposide and response rate or survival for limited or extensive stage disease. Furthermore, no consistent correlation in relative dose intensity of any individual drugs and outcome was observed.[37]

Weekly chemotherapy have not in phase III-studies for patients with SCLC demonstrated any advantage compared to standard treatment given at intervals of three weeks.[28, 35] Comparisson of dose intensity given in weekly programs compared to standard programs have shown that weekly delivery of myelosuppressive chemotherapy does not allow recovery of granulocytes. However, it is still too early to say whether this approach is significant beneficial for patients with SCLC.

Dose intensity with bone marrow support

High dose chemotherapy with autologous bone marrow transplantation ABMT have been studied by

several groups. The largest studies by Souhami et al[38] and Smith et al[39] reported median relapse free survival and overall survival similar to those associated with standard chemotherapy approaches. In a randomized study of intensive chemotherapy and ABMT by Humblet et al[40] they found the complete response (CP) rate increasing from 39 % to 79 % with the intensive post induction chemotherapy. The relapse free survival was significantly increased in the group as a whole and in a subset of patients with limited stage disease.

A recent study by Elias et al[41] has again evaluated the effects of intensive chemotherapy with bone marrow support in patients with SCLC who were in complete or partial response following conventional chemotherapy. In this phase II study, however, patient selection and consolidative chemotherapy were chosen to address some of the prior issues raised with earlier trials. Nineteen patients with limited stage SCLC who had achieved a partial or complete response to first live conventional dose chemotherapy were treated with high dose cyclophosphamide, cisplatin and carmustine with autologous bone marrow support and thoracic and cranial radiotherapy. After high dose chemotherapy, 15 of 19 were in complete response with a one and two year survival rate of 73 % and 53 %, respectively.

The role of colony stimulating factors in small cell lung cancer

The colony stimulating factors (CSFs) are glycoprotein hormones that stimulate proliferation and differentiation of hematopoetic progenitor cells. Possible uses for these agents in the treatment of small cell lung cancer are to allow possible dose escalation of myelosupressive chemotherapy agents, to protect patients prophylactically from febrile neutropenia prior to standard chemotherapy and to speed neutrophil recovery following chemotherapy.

The effect of prophylactic granulocyte – colony stimulating factors (G-CSF) has been studied by Crawford et al.[42] This randomized placebo controlled study of patients receiving chemotherapy for SCLC demonstrated that prophylactic G-CSF can significantly reduce neutropenia and infective complications following standard-dose chemotherapy. Patients received standard dose cyclophosphamide, doxorubicin and etoposide with placebo or G-CSF 230 microgram/m^2 on days 4–17. One or more febrile neutropenic episodes occurred in 77 % of the placebo group but in only 40 % of the G-CSF group. The duration of neutropenia (neutrophil count < 0.5 × 10^9/l) was 6 days with placebo and only 1 day with G-CSF. The number and duration of hospital admissions were less in the G-CSF group. However, regarding tumor respons and survival there was no difference in either arm. The side effect mild to moderate bone pain was documented in 20 % of patients given G-CSF. Another prospective randomized trial was conducted in patients with SCLC receiving PE alternating with ifosfamide and doxorubicin to determine whether G-CSF could increase the received dose intensity of weekly chemotherapy. G-CSF decreased dose reductions due to neutropenia, but did not result in increased dose intensity due to non-hematologic toxicities.[43] Other studies have suggested that the incidence of neutropenic fever with standard dose chemotherapy is low (about 18 %) and that routine use of G-CSF in this setting is expensive and not associated with a cost savings or therapeutic benefit.[44] In a recently published study by Bunn et al patients with limited stege SCLC receiving concurrent chemotherapy and radiation therapy, patients randomized to receive granulocyte-macrophage colony stimulating factor (GM-CSF) had more infections, more days febrile and a significant increase in thrombocytopenia compared to those randomized to no GM-CSF and there was no benefit in response rates or survival time by using GM-CSF.[45]

Duration of chemotherapy and treatment of progressive tumors

In the beginning of the chemotherapy era it was though that more and longer chemotherapy was better, and treatment durations of 12–18 months was not unusual.[2] However, as mentioned earlier the principle of prolonged administration of chemotherapy in patients who responded to treatment did not improve survival.[30, 33, 34, 36] The most usual treatment duration today is about 6 months, but no randomized studies have yet established the most optimal treatment duration. Small-cell carcinoma that progresses during or after initial chemotherapy is usually refractory to further treatment and is always incurable; however, the likelihood of disease regression and palliation with subsequent chemotherapy in patients who have previously responded is greater if tumor regrowth is preceded by at least a few months of no treatment.[10, 47, 48] Chemotherapy

should therefore be discontinued after four to six months in patients who respond and then resumed at relapse if clinically appropriate. Thus, the success of second line chemotherapy is dependent on multiple factors including:

– the interval between cessation of primary therapy and the detection of recurrence
– the nature of the response to primary therapy and
– the composition of the primary chemotherapy.

Long-term survival

SCLC is an extremely responsive tumor. The introduction of combination chemotherapy as the principle form for treatment of SCLC led to an increase in median survival and suggestion that a significant proportion of patients might be cured. Unfortunately, the results from long-term survival studies indicate that only a small proportion of patients with SCLC are cured by current treatment. Souhami and Law reported on 3681 cases of SCLC treated in major centres in UK and found that only 3 % were alive at seven years (3,6 % LD, 1 % ED).[49] The results from the clinical trials in the Copenhagen Lung Cancer Study Group including 1714 patients were comparable with the results from the UK. The rate of 5-years survivors was 3,5 %. Among the 828 patients with limited disease 40 patients (4.8 %) became long-term survivors and 20 of 886 patients (2.3 %) of the ED patients. The 10-years survival rate was 1,8 %.[50] These results document that patients with small cell lung cancer continue to relapse up to and occasionally after 5 years.

Beyond 6 years other smoking-related diseases become the major cause of death. Particularly chronic bronchitis, vascular disease and smoking related cancer. These survival data although demonstrating the bad long term prognosis of SCLC do not indicate that treatment is not worthwhile. Some patients, most of them initially presented with limited disease, are cured. However, for the vast majority of patients treatment is palliative and for most of the patients chemotherapy undoubtedly provides effective palliation of symptoms with prolongation of short time survival.

New drugs

Over the past five years a number of new agents with activity against lung cancer have been identified. The relative resistance of SCLC to second line therapy has raised a considerable dilema in the development of strategies to identify new drugs to treat the disease. When new agents are tested in previously treated patients, response rates are lower than they might be in untreated patients, and it is possible that potentially active agents might be missed. Ideally new agents should be tested in previously untreated patients.

An alternative approach has been to incorporate new agent as part of combination regimen or to offer new agents to those patients who have not received therapy for 3 or more months.

Taxanes

The taxanes, representated by the prototypic agent paclitaxel (Taxol) and the semisynthetic analogue docetacxel (Taxotere) are the first class of anti-microtubule agents developed since the vinca alkaloids.

Paclitaxel: has been evaluated in two phase II-studies involving previously untreated patients with extensive-stage SCLC.[51, 52] In one study preliminare published by Eastern Cooperative Oncology Group (ECOG) 32 evaluable patients were treated with Taxol 250 mg/m^2 intravenously over 24h every 3 weeks. There were no patients with CR, while PR was found in 11 patients (34 %). However, further 3 patients had a greater than 50 % shrinkage of their disease, but did not have the 4 week follow up which is a requirement of PR. In another study 37 evaluable patients were treated. There were no CR's, but 15 patients had PR (41 %). There are several ongoing phase II studies with paclitaxel. In two recently published preliminary results from treatment with paclitaxel in combination with cis-platin/carboplatin and etoposide high response rates were reported.[53, 54] However, it is too short observation for long term results.

Docetaxel: In an EORTC-study, Smyth et al[55] performed a phase II-trial of docetaxel 100 mg/m^2 i.v. as a 1 h-infusion every 3 weeks. Among 27 patients (23 patients had prior treatment) 5 of 18 (28 %) had PR.

The camptothecins

The topoisomerate I targeting agents represent one of the most promising classes of antineoplastic agents under development.

CPT-11 (irinotecan) is a camptothecin derivate with greated aqueons solubility than comptothecin.

In phase I studies the principal dose-limiting effect on all schedules has been myelosuppression, but non-hematologic side effects like diarrhea have avoided dose escalation. Masuda et al[56] studied CPT-11 in 15 previously treated evaluable patients with SCLC and 47 % had a PR. Fujiwara et al[57] evaluated CPT-11 plus cis-platin in previously untreated patients with SCLC. Among 18 patients with LD evaluable for response there were 4 patients with CR (22 %) and 10 PR's (50 %). Among 14 patients with ED there were 3 patients with CR's (21 %) and 8 patients with PR (57 %).

Topotecan: is a water soluble comptothecin analogue with topoisomerase I-targeting activity. The drug's dose-limiting toxicity in phase I-studies was neutropenia and in some cases also trombocytopenia. In an ECOG-study[58] 41 patients with previosly untreated extensive disease SCLC were treated with topotecan 2.0 mg/m^2/day i.v. 5 days every 3 weeks. PR was seen in 39 % and in a study of Ardizzoni et al[59] 29 previously untreated patients were treated with 1.5 mg/m^2/day × 5 every 3 weeks and 10 % had CR and 25 % PR.

Gemcitabine

Gemcitabine is a new nucleoside analogue antimetabolite. In phase I-trials the dose-limiting toxicity was myelosuppression, mainly trombocytopenia and anemia. In a NCI/Canada study[60] gemcitabine was evaluated in previously untreated patients (23 evaluable) and there was one CR (4 %) and six patients had PR (26 %).

However, all the phase II-studies with the above mentioned new drug have relatively small numbers of patients and future approach should be to evaluate these new drugs in combination with the other active drugs for the treatment of SCLC.

Combination of thoracic radiotherapy and chemotherapy

The role of mediastinal irradiation in the treatmenf of patients with SCLC have been discussed for many years. Meta-analyses indicate that the addition of radiotherapy to combination chemotherapy has improved survival significantly for the patients with **limited** small cell lung cancer.[61] Hovewer, the randomized trials that formed the bases for these analyses were from early this decade and the previous one. Most of the chemotherapy regimens were cyclohosphamide/doxorubicin based and none of them had up front cis-platin based chemotherapy programs. Thus, the chemotherapy used in the trials are today considered as sub-optimal. The combined treatment modality has resulted in excess toxocity, which is likely to be related to chemotherapy and radiotherapy factors and/or combined modality interactions. The meta-analyses could not establish that either sequence, concurrent or sequential treatment was optimal.

The combination chemotherapy including cis-platin (PI) and etoposide (E) is today the cornerstone of the systemic treatment of patients with SCLC. Turisi has recently reviewed the radiotherapy factors and discussed the state of art with the combination of thoracal irradiation and PE-based chemotherapy in relation to dose of irraditation, volume, fraction and timing.[62] Most centers today are using mediastinal irradiation combined with PE-based chemotherapy regimen as the cornerstone of therapy for patients with limited SCLC. However, both local and systemic failures avoid the therapeutic success.

While the **local** failures might be reduced by more optimal given radiotherapy (better targeting, increasing intensity or total dose, hyperfractionation etc.) the toxocity, especially esophagittis is still a significant problem, but the **systemic** failures as well is a documentation of the need for a better systemic treatment.

Treatment of brain metastases

While the brain was thought to be a sanctuary site in the chemotherapy of SCLC for many years, this concept has been changed. Several studies have demonstrated a high response rate on the initial brain metastases when treated with chemotherapy alone, and when evaluated by subsequent. CT-scans the response rates in the brain is similar to the response rates extracranially.[63] Thus, the treatment strategy today for patients who present with brain metastases in the initial phase of the disease course, is systemic treatment with the same chemotherapy as used for extracarnial disease.

However, the treatment of brain metastases diagnosed **during** chemotherapy is not quite clear. At that stage the tumor might not be sensitive to the given chemotherapy and the treatment strategy must depend on several factors: 1. Are the extracranial

disease under control 2. Can the symptoms be controlled by steroids alone? and 3. What is the patients performance status and prognosis?

If the extracranial disease is under control on chemotherapy and/or radiotherapy cranial irradiation seems reasonable. However, if the patient develop brain metastases and have progressive disease outside the brain only symptomatic treatment with steroids seems reasonable.

Prophylactic cranial irradiation

Brain metastases is a serious clinical problem in patients with SCLC. The brain is a frequent site of metastasis and is clinical evident in about 10 % of patients at tim of primary diagnosis and demonstrated in about 50 % of the patients at time of autopsy.[64]

The possibility of using prophylactic cranial irradiation (PCI) in the management of SCLC patients was suggested already in 1973,[65] based on an early prediction of an increase in the incidence of brain metastases with increased survival. However, still in 1995 this question is not completely solved. The topic has recently been reviewed in details elsewhere.[66]

Until now there has not been demonstrated any significant impact of survival – not either for patients who receive CR on systemic treatment – by using PCI.

The problem with the published studies has been the small number of patients with CR available for the PCI-studies and the lack of randomization. Currently, there are some ongoing multicenter trials, which hopefully will include large enough number of patients to obtain sufficient statistical power to detect a potential survival benefit by using PCI. Presently, it is general agreement that PCI is not justified in patients who are not in CR. The answer whether PCI should be given recommended routinely to patients in CR or not has to await the ongoing trials.

Future strategy in the treatment of SCLC

During the past 10–15 years the treatment of SCLC has improved and the existing chemotherapy with or without thoracic radiotherapy are capable of effecting marked prolongation of survival, especially for patients presenting with limited disease with a median survival close to 20 months, 2 years about 40% and occasional cures. However, further research is needed to improve especially the systemic treatment. However, conventional chemotherapy with well known cytotoxic drugs in different combinations have not made a breakthrough in the treatment of patients with SCLC. Therefore, future investigations have to focus on several new areas including. 1. new drugs prefereably with novel mechanisms of action. 2. Modulations of drug resistance. 3.

Biological therapy, 4. Gene therapy and 5. Prevention of secondary malignancies (chemoprevention).

New drugs are discussed above. Of special interest would be to test the new drugs in combination with the well known drugs with verified effect in SCLC. There are ongoing studies for patients with extensive SCLC using sequential treatment of Topoisomerate I and II inhibitors.[67]

Despite the fact that most of the SCLC tumors are chemosensitive the major obstacle is the drug resistance. There are several mechanisms by which SCLC tumors become resistent of the cytotoxic agents. The presence of p-glycoprotein does not appear to be common in SCLC.[68, 69] Nevertheless, p-glycoprotein inhibitors should be included in the future investigational strategy of therapy as well as strategies designed to alter the topoisomerase level, which play an important role in the DNA replication and repair. Recently, bcl-2 transcripts and protein have been found to be expressed in 5/6 SCLC cell lines,[70] and transfection of bcl-2 into a SCLC cell line has shown to increase chemoresistance.[71] These mechanisms are further studied and might be included in the future treatment strategy.

It has been known for many years that SCLC is associated with production of several peptide hormones, which function as autorine growth factors such as gastrin releasing peptide (GRP), insulin-like growht factor (IGF-1), transforming growth factors (TGF-beta) and several others.[72] Monoclonal antibody to GRP has in a preliminary study shown to give complete response in a patient with SCLC,[73] and early clinical studies with other peptide antigens, i.e. somatostatin analogue are ongoing.

Mutatiton of the gene p-53 have been found in virtually and small cell lung cancer cell lines and in most of the tumors from the patients, and more than half of SCLC cell lines fail to express retinoblastoma gene protein product.[72] Correction of these

abnormalities through gene therapy might play a role in the future strategy.

As previously mentioned a high percentage of the long-term survivors from SCLC develop a secondary malignancy, most often a tobacco-related cancer.[50] Therefore, chemoprevention studies are warranted in the long-term survivors of SCLC and ongoing studies with retinoid acids for patients with lung cancer seem promising.[74]

References

1. Stanley K, Stjernsward J. Lung cancer – a worldwide problem. 1989; *Chest* **96:** 1S–5S.

2. Hansen HH. Management of small cell cancer of the lung. *Lancet* 1992; **339:** 846–9.

3. Grant S, Gralla R, Kris M et al. Single agent chemotherapy trials in small cell lung cancer, 1970 to 1990: The case for studies in previously treated patients. *J Clin Oncol* 1992; **10:** 484–98.

4. Edmondson J, Lagakos S, Selawry O et al. Cyclophosphamide and CCNU in the treatment of inoperable small cell carcinoma and adenocarcinoma of the lung. *Cancer Treat Rep* 1976; **60:** 925–32.

5. Lowenbraun S, Bartolucci A, Smalley R et al. The superiority of combination chemotherapy over single agent chemotherapy in small cell lung carcinoma. *Cancer* 1979; **44:** 406–13.

6. Fukuoka M, Furuse K, Saijo N et al. Randomized trial of cyclophosphamide, doxorubicin and vincristine versus cisplatin and etoposide versus alternation of these regimens in small-cell lung lancer. *J Natl Cancer Inst* 1991; **83:** 855–61.

7. Hirsch FR, Hansen HH, Hansen M et al. The superiority of combination chemotherapy including etoposide based on in vivo cell cycle analysis in the treatmen of extensive small-cell lung cancer: A randomized trial of 288 consecutive patients. *J Clin Oncol* 1987; **5**: 585-91.

8. Johnson DH, Hainsworth JD, Hande KR et al. Current status of etoposide in the management of small cell lung cancer. *Cancer* 1991; **67**: 231–44.

9. Roth BJ, Johnson DH, Einhorn LH et al. Randomized study of cyclophosphamide, doxorubicin and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer. A phase III trial of the Southeastern Cancer Study Group. *J Clin Oncol* 1992; **10**: 282–91.

10. Batist G, Carney DN, Cowan KH et al. Etoposide (VP-16) and cisplatin in previously treated small-cell lung cancer: clinical trial and in vitro correlates. *J Clin Oncol* 1986; **4**: 982–6.

11. Carney DN. Carboplatin/etoposide combination chemotherapy in the treatment of poor prognosis patients with small cell lung cancer. *Lung Cancer* 1995; **12**, suppl, **3**: 77–83.

12. Skarlos DV, Samantas E, Kosmidis P et al. Randomized comparison of etoposide-cisplatin vs. etoposide-carboplatin and irraditation in small celll lung cancer: a Hellenic cooperative oncology group study. *Ann Oncol* 1994; **5**: 601–7.

13. Goldie JH, Goldman AJ, Gudauskas GA. Rationale for the use of alternating non-cross-resistant chemotherapy. *Cancer Treatment Rep* 1982; **66**: 439–49.

14. Evans WK, Feld R, Murray N et al. Superiority of alternating non-cross-resistant chemotherapy in extensive small cell lung cancer. *Ann Int Med* 1987; **107**: 451–8.

15. Einhorn LH, Crawford J, Birch R et al. Cis-platin plus etoposide consolidation following cyclophosphamide, doxorubicin and vincristine in limited small cell lung cancer. *J Clin Oncol* 1988; **6**: 451–6.

16. Dombernowsky P. Primary treatment of small cell lung cancer. In: Hirsch FR ed. *Lung Cancer: Status and future perspectives*. Bristol-Myers Squibb, 1993: 83–100.

17. Jensen PB. Personal communications.

18. Hirsch FR, Dombernowsky P, Hansen HH. Treatment of small cell lung cancer: The Copenhagen Experience. *Anticancer Res* 1994; **14**: 317–20.

19. Bork E, Ersbøll J, Dombernowsky P et al. Teniposide and etoposide in previously untreated small-cell lung cancer: a randomized study. *J Clin Oncol* 1991; **9**: 1627–31.

20. Carney DN, Grogan L, Smit EF et al. Single-agent oral etoposide for elderly small cell lung cancer patients. *Semin Oncol* 1990; **17**, suppl, **2**: 49–53.

21. Carney DN. Carboplatin/etoposide combination chemotherapy in the treatment of poor prognosis patients with small cell lung cancer. *Lung Cancer* 1995; **12**, suppl, **3**: 77–83.

22. Slevin M, Clark PI, Joel SP et al. A randomized trial to evaluate the effect of schedule on the activity of etoposide in small cell lung cancer. *J Clin Oncol* 1989; **7** 1333.

23. Cohen M, Creaven P, Fossieck BJ et al. Intensive chemotherapy of small cell bronchogenic carcinoma. *Cancer Treat Rep* 1977; **61**: 349–54.

24. Abeloff M, Ettinger D, Order S et al. Intensive induction chemotherapy in 54 patients with small cell carcinoma of the lung. *Cancer Treat Rep* 1981; **65**: 639–46.

25. Figueredo T, Hryniuk W, Strautmanis I et al. Co-trimoxazole prophylaxis during high-dose chemotherapy of small-cell lung cancer. *J Clin Oncol* 1985; **3**: 54–64.

26. Ihde D, Mulshine J, Kramer B et al. Randomized trial of high vs. standard dose etoposide (VP 16) and cisplatin in extensive stage small cell lung cancer (SCLC). *Proc Amer Soc Clin Oncol* 1991; **10**: 240.

27. Ihde D, Mulchine J, Kramer B et al. Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lunc cancer. *J Clin Oncol* 1994; **12**: 2022–34.

28. Sculier J, Paesmans M, Bureau G et al. Multiple-drug weekly chemotherapy versus standard combination regimen in small-cell lung cancer. A phase II randomized study conducted by the European Lung Cancer Wrokshop Party. *J Clin Oncol* 1993; **11**: 1858–65.

29. Ihde D, Mulshine J, Kramer B et al. Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 1994; **12**: 2022–34.

30. Ettinger DS, Finkelstein DM, Abeloff MD et al. A randomized comparison of standard chemotherapy versus alternating chemotherapy and maintenance versus no maintenance therapy for extensive-stage small-ceel lung cancer: A phase III study of the Eastern Cooperative Oncology Group. *J Clin Oncol* 1990; **8**: 230–240.

31. Giaccone G, Dalesio O, McVie G et al. Maintenance chemotherapy in small-cell lung cancer: long term results of a randomized trial. *J Clin Oncol* 1993; **11**: 1230–40.

32. Party LCW. Controlled trial of twelve versus six courses of chemotherapy in the treatment of small-cell lung cancer: Report to the Medical Research Council by its Lung Cancer Working Party. *Br J Cancers* 1989, **59**: 584–90.

33. Spiro S, Souhami R, Geddes D et al. Duration of chemotherapy in small cell lung cancer: A Cancer Resarch Campaign Trial. *Br J Cancer* 1989; **59**: 578–83.

34. Splinter T. EORTC 08825. Induction vs induction plus maintenance chemotherapy (CT) in small cell lung cancer (SCLC). Definitive evaluation. Proc ASCO 7: 202, 1988.

35. Miles D, Souhami R, Spiro S et al. A randomized trial comparing »standard« 3 weekly with chemotherapy (C/T) in patients (PTS) with small cell lung cancer (SCLC). *Proc ASCO* 1992; **11**: 289.

36. Arriagada R, le Chevalier T, Pignon J-P et al. Initial chemotherapeutic doses and survival in patients with limited small-cell lung cancer. *N Engl J Med* 1993; **329**: 1848–52.

37. Klasa R, Murray N and Coldman A. Dose-intensity meta-analysis of chemotherapy regimens in small-cell carcinoma of the lung. *J Clin Oncol* 1991; **9**: 499–508.

38. Souhami R, Hajichristou H, Miles D et al. Intensive chemotherapy with autologous bone marrow transplantation for small-cell lung cancer. *Cancer Chemother Pharmacol* 1989; **24**: 321–5.

39. Smith I, Evans B, Harland S et al. High-dose cyclophosphamide with autologous bone marrow rescue after conventional chemotherapy in treatment of small-cell lung carcinoma. *Cancer Chemother Pharmacol* 1985; **14**: 120–4.

40. Humblet Y, Symann M, Bosly A et al. Late intensification chemotherapy with autologous bone marrow transplantation in selected small-cell carcinoma of the lung: A randomized study. *J Clin Oncol* 1987; **5**: 1864–73.

41. Elias A, Ayash L, Frei III E et al. Intensive combined modality therapy form limited-stage small-cell lung cancer. *J Natl Cancer Inst* 1993; **85**: 559–66.

42. Crawford J, Ozer H, Stoller R et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients will small-cell lung cancer. *N Engl J Med* 1991; **325**: 164–170.

43. Miles D, Fogarty O, Ash C et al. Received dose-intensity. A randomized trial of weekly chemotherapy with and without granulocyte colony-stimulating factor in small-cell lung cancer. *J Clin Oncol* 1994; **12**: 77–82.

44. Nichols C, Fox Em Roth Be et al. Incidence of neutropenic fever in patients treated with standard-dose combination chemotherapy for small-cell lung cancer and the cost impact of treatment with granulocyte colony-stimulating factor. *J Clin Oncol* 1994; **12**: 1245–50.

45. Bunn P, Crowley J, Kelly K et al. Chemoradiotherapy with or without granulocyte-macrophage colony stimulating factor in the treatment of limited stage small- cell lung cancer: A prospective phase III randomized study of the southwest oncology group. *J Clin Oncol* 1995; **13**: 1632--41.

46. Controlled trial of twelve versus six courses of chemotherapy in the treatment of small-cell lung cancer: report to the Medical Research Council by its Lung Cancer Working Party. *Br J Cancer* 1989; **59**: 584–90.

47. Giaccone G, Donadio M, Bonardi G et al. Teniposide in the treatment of small-cell lung cancer: the influence of prior chemotherapy. *J Clin Oncol* 1988; **6**: 1264–70.

48. Johnson DH, Greco FA, Strupp J et al. Prolonged administration of oral etoposide in patients with relapsed or refractory small-cell lung cancer: a phase II trial. *J Clin Oncol* 1990; **8**: 1613–7.

49. Souhami RL, Law K. Longevity in small-cell lung cancer:: A report to the Lung Cancer Subcommitteee of the United Kingdom Coordinating Committee for Cancer Research. *Br J Cancer* 1990; **61**: 584–9.

50. Lassen U, Østerlind K, Hansen M et al. Long-term survival in small-cell lung cancer: Posteatment characheristics in patients surviving 5 to 18 + years. An analysis of 1714 consecutive patients. *J Clin Oncol* 1995; **13**: 1215–20.

51. Ettinger DS, Finkelstein DM, Sarma R et al. Phase II study of taxol in patients (pts) with extensive-stage smal-cell lung cancer (SCLC): an Eastern Cooperative Oncology Group Study. *Proc Am Soc Clin Oncol* 1993; **12**: 329.

52. Kirschling RJ, Jung SH, Jett JR for the North Central Cancer Treatment Group. A phase II trial of taxol and G-CSF in previously untreated patients with exentive-stage small cell lung cancer (SCLC). *Proc Am Soc Clin Oncol* 1994; **13**: 326.

53. Levitan N, McKenney J, Tahsildar H et al. Results of a phase I dose escalation trial of paclitaxel, etoposide and cisplatin followed by lilgramstim in the treatment of patients with extensive stage small-cell lung cancer. *Proc Bristol-Myers Squibb Symposium.* Am Soc Clin Oncol, 1995: 99.

54. Hainsworth JD, McKay CE, Miller PS et al. Treatment of small-cell lung cancer (SCLC) with paclitaxel (one hour infusion), carboplatin, and low dose daily etoposide. *Proc Bristol-Myers Squibb Symposium,* Am Soc Clin Oncol, 1995: 100.

55. Smyth JF, Bowman A, Smith I et al. Taxotere is active in small-cell lung cancer (SCLC). A phase II trial of the EORTC Early Clinical Trials Group (ECTG). *Eur J Cancer* 1993; **29A,** suppl, **6:** 154.

56. Masuda N, Fukuoka, Kusunoki Y et al. A new derivate of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. *J Clin Oncol* 1992; **10**: 1225–9.

57. Fujiwara Y, Yamakido M, Fukuoka M et al. Phase II study of irinotecan (CPT-11) and cisplatin (CDDP) in patients with small-cell lung cancer (SCLC). *Proc Am Soc Clin Oncol* 1994; **13**: 330.

58. Schiller JH, Kim K, Johnson D for the Eastern Cooperative Oncology Group. Phase II study of topotecan in extensive stage small cell lung cancer. *Proc Soc Clin Oncol* 1994; **13**: 330.

59. Ardizzoni A, Hansen H, Dombernowsky P et al. Phase II study of topotecan in pretreated small cell lung cancer (SCLC). *Proc Am Soc Clin Oncol* 1994; **13**: 336.

60. Cormier Y, Eisenhauer Ea, Muldal A et al. Gemcitabine is an active new agent in previously untreated extensive small cell lung cancer (SCLC). *Ann Oncol* 1994; **5**: 283–5.

61. Pignon J-P, Arriagada R, Ihde D et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med* 1992; **327**: 1618–24.

62. Turisi AT. Combined platinum etoposide with radiation therapy in limited stage small cell lung cancer: an effective treatment strategy. *Lung Cancer* 1995; **12**: suppl, **3**: S41–S51.

63. Kristensen CA, Kristjansen PEG, Hansen HH. Systemic chemotherapy of brain metastases from small cell lung cancer – A review. *J Clin Oncol* 1992; **10**: 1498–502.

64. Hirsch FR, Paulson OB, Hansen HH and Olesen Larsen S. Intracranial metastases in small cell carcinoma of the lung. *Cancer* 1983; **51**: 933–7.

65. Hansen HH. Should initial treatment of small cell lung-carcinoma include systemic chemotherapy and brain irradiation. *Cancer Chem Rep* 1973; **4**: 239–41.

66. Kristjansen PEG, Hansen HH. Prophylactic cranial irradiation in small cell lung cancer – an update. *Lung Cancer* 1995; **12**: suppl **3**: S23–S40.

67. Johnson DH. Future dirctions in the management of small cell lung cancer. *Lung Cancer* 1995; **12,** suppl **3**: S71–S75.

68. Lai S-L, Goldstein L, Gottesman MM et al. MDR1 gene expression in lung cancer. *J Natl Cancer Inst* 1989; **81**: 1144–50.

69. Poupon MF, Arvelo F, Goguel AF et al. Response of small-cell lung cancer xenografs to chemotherapy: multidrug resistance and direct clinical corrrelates. *J Natl Cancer Inst* 1993; **85**: 2023–9.

70. Ikegaki N, Latsuata, M, Minna J and Tsujimoto Y. Expression of bcl-2 in small cell lung carcinoma cells. *Cancer Res* 1994; **54**: 6–8.

71. Ohmori T, Podack ER, Nishio K et al. Apoptosis of lung cancer cells caused by some anti-cancer agents (MMC, CPT-11, ADM), inhibited by bd-2. *Biochem Biophys Res Commun* 1993; **192**: 30–6.

72. Richardson GE, Johnson BE. The biology of lung cancer. *Semin Oncol* 1993: **20**: 105–27.

73. Kelly MJ, Avis RI, Linnoila RI et al. Complete response in a patient with small cell lung cancer treated on a phase II trial using a murine monoclonal antibody (2A11) directed against gastrin releasing peptide (GRP). *Proc Am Soc Clin Oncol* 1993; **12**: 339.

74. Hong WK, Benner SE and Lippman SM. Retinoid chemoprevention of lung cancer. *Lung Cancer,* 1994; **11:** suppl **2**: 92–3.