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Chemotherapy in small cell lung cancer

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ABSTRACT: Chemotherapy is the backbone in the treatment of small cell lung cancer (SCLC) and radiotherapy is an important adjunct in limited stage disease. The role of chest irradiation is now documented in three meta-analysis, based on the same body of data. Trials on timing, scheduling and fractionation could have followed a more stringent development line but altogether, the highest efficacy seems to be obtained with early, concurrent twice-daily chest irradiation. Patients in complete remission should have prophylactic cranial irradiation, which reduces the risk of brain metastases and of death from SCLC.

Four series of chemotherapy seem to be sufficient in limited-stage disease while six is recommended in extensive disease. The combination of etoposide plus cis- or carboplatin is appropriate in both stages and addition of other agents has no clinically important impact on the survival. Use of haematological growth factors such as granulocyte colony stimulating factor (G-CSF) and granulocyte macrophage colony stimulating factor (GM-CSF) may enable higher doses or more frequent dosage. Three randomized trials on GM-CSF showed a negative outcome while G-CSF support may result in better survival rates, but a more cost-efficient policy must be found. High-dose chemotherapy plus haematological stem-cell support is still under investigation but disappointing long-term survival rates means there is not much optimism for this strategy.

New strategies in general are requested in the treatment of extensive-stage disease and of elderly patients. Phase II trials suggest that good-risk patients with extensive disease should be treated aggressively, intermediate-risk patients more gently, and palliation must be the primary aim in the treatment of poor-risk patients. In elderly patients impressive survival rates are obtained with 3–4 series of chemotherapy and radiation delivered in 5–10 fractions.

A number of new agents are active but more trials are required before each has found a place, if any, in the treatment of small cell lung cancer. To conclude, the randomized trial is still an important instrument in clinical oncology, and trials in small cell lung cancer must be large, which is why the cooperation of organizations and multicentres is urgent.
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Chemotherapy is the keystone in the treatment of small cell lung cancer (SCLC). Objective remission and good palliation is achieved in ~80% of the patients, but the remissions are in general short (mean <1 yr), and few are cured. As an example, 5- and 10-yr survival rates, in 1,714 SCLC patients treated in trials in Copenhagen during 1973–1987, were only 3.5 and 1.8%, respectively [1]. Only 184 (11%) of these patients received chest irradiation. In those days the role of radiotherapy was still an issue of debate, but two meta-analyses, published in 1992 [2], ended the discussion. Search for an optimal schedule and timing of the radiotherapy has prompted several randomized trials and the sum of the data from these trials suggests that radiotherapy should be given early, concurrently and twice daily [3]. Irradiation of the adrenals has never proved worthwhile [4] while prophylactic cranial irradiation (PCI) in complete remission patients has a significant positive impact on the prognosis, proven in a meta-analysis [5]. Trials aiming to find the optimal dose and indications for PCI are under way.

Sixty to 65% of patients with SCLC have extensive disease at the time of diagnosis. Spread of disease prevents appropriate limits for a chest radiation field, and the prognosis is significantly reduced. Many efforts have been undertaken to improve treatment outcome in extensive stage disease, especially trials on high dose or dose-accelerated regimes, but the outcome has been disappointing. High-dose chemotherapy plus haematological stem-cell support has found a place in haematology, such as in the treatment of recurrent lymphomas, and the strategy has also been investigated as a first-line treatment for good-prognosis patients with SCLC, mostly in phase II trials. High complete response rates are obtained, but there is considerable toxicity and the long-term survival rates are not improved.

Twenty-five per cent of patients with SCLC are aged >74 yrs and most of these patients may not tolerate combination chemotherapy. But elderly people are less fatalistic today, they expect treatment for conditions such as cancer, and although there have been some trials on older patients during the last 10–15 yrs, the treatment options are limited.

The fact that age has not proved to be an important prognostic factor in a large series [6] suggests that treatment for cure may be a reasonable policy in some elderly patients. The prognosis in SCLC is influenced by stage of disease plus other clinical characteristics such as performance status (PS) and plasma lactate dehydrogenase (LDH), followed by plasma sodium, anaemia, plasma albumin, alkaline phosphatase, and bicarbonate [6–9]. Prognostic factors, especially PS and LDH, are important as in- and exclusion criteria in treatment trials, as stratification or balancing variables in randomized trials, and as potential end point confounders. In that context further standardization is warranted, a task which has recently been undertaken by a staging committee under the International Association for the Study of Lung Cancer (IASLC).

Surgery is seldom possible in SCLC [10] and explorative thoracotomies are rare today due to routine use of percutaneous lung biopsies and modern imaging techniques to guide invasive procedures if necessary. In addition mediastinoscopy has had a renaissance in the staging of lung cancer [11]. More than 85% of SCLC patients have mediastinal lymph-node metastases [12] and in a time when better local control of the tumour seems possible, due to improved radiotherapy most will agree that surgery has had its role in the treatment of SCLC.

A number of new cytotoxic drugs have been investigated in the last decade including an antimetabolite (gemcitabine), taxanes and topoisomerase I inhibitors. Although the trials have resulted in reasonable developments, a complete understanding of the best way to use these agents is needed.

Treatment strategies in small cell lung cancer

Clinical research in to the treatment of SCLC is not driven by the same optimism as it was 20-yrs-ago but trials on new agents and new biological principles in conjunction with the classical regimes are always under way. With trials carried out by laboratories, who never lose interest, or initiated by drug companies, often in an international set up. Local trials on feasibility and practical, clinical characteristics of treatment regimes for SCLC also occur, often in certain categories such as elderly or poor-risk patients. Survival is still the major end point in trials on SCLC but outcome variables also include measures of palliation, reduced toxicity, days of hospitalization and cost-efficacy ratio. New strategies, based on a fast developing, molecular biological understanding of cancer, will certainly get an increasing impact on the clinical drive for a better treatment. Biological strategies have been tested in clinical practice since the introduction of chemotherapy three-decades ago. The classical example is the Goldie-Coldman hypothesis [13] from which a computer growth simulation model showed that alternating chemotherapy with non-crossresistant regimes would increase the chances of a successful outcome. The principle, however, turned out to have only a restricted impact in SCLC, detectable in extensive but not in limited stage disease [14–16].

Intensive and high-dose chemotherapy has found a place in the treatment of haematological neoplasms and achievements from this field plus development of the blood stem-cell rescue technology have stimulated trials on this strategy in solid tumours, including SCLC. Whether or not high-dose chemotherapy has a role in the treatment of SCLC is still an open question.

Radiotherapy is now a standard in the treatment of limited stage SCLC. Current investigations focus on the timing, fractionation and interaction with concurrent chemotherapy. PCI reduces the risk of brain metastases [17]. The efficacy seems to be dose dependant and the balance point between maximal effect and minimal-late toxicity has to be found.

New cytotoxic drugs are steadily being investigated in various combination regimens, often in trials organized by the manufacturing drug company. The steering of this process is a big challenge to all clinical oncologists. Similar conditions are typical for clinical investigations on biological processes activated by the cancer to enable invasion, nourishment and spread, which include proteolysis, angiogenesis and interaction with the immune system.

Treatment of limited disease

Evidence for the usefulness of chest irradiation in limited-stage SCLC was established in two meta-analyses published in 1992 [2, 18]. The body of data for the two investigations was essentially the same, *i.e.* outcome of randomized trials from the period 1975–1989 including a total of some 2000 patients. One group retrieved the raw data [2] while the other skimmed the publications. The outcomes, however, were much alike, both proving a significant improvement in survival. As an example, the 3-yr survival rates in Pignon's study were 14.3% in 1,111 patients assigned to combined modality therapy compared to 8.9% in 992 patients treated with chemotherapy alone. The 3-yr survival rates in recent trials are ~20% and rates >30% are reported. Several factors may contribute to higher rates. 1) Stage migration as a result of new imaging technologies in staging of lung cancer such as spiral computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) scanners. 2) Chemotherapy in recent trials is based on the combination of cisplatin+etoposide (PE), which is more efficacious than some of the odd combinations used in the 1970–1980s [19] and less toxic than regimes including doxorubicine when delivered concurrently with the irradiation. 3) Most trials today include prophylactic brain irradiation to complete responders. 4) Timing, dosage, fractionation and computer-assisted CT

Table 1. – Conventional thoracic radiotherapy regimes

First author [ref. no.]	Radiation	Schedule week	Concurrent	Arm	Patients n	Chemotherapy regime
WORK [21]	45 Gy/22 F	1–2 & 6–7	No	Early	99	P: 60 mg·m^{-2} day 1
	Split course	18–19 & 23–24	No	Late	100	E: 120 mg·m^{-2} day 1–3
GREGOR [22]	50 Gy/20 F	6, 10, 14, 18	No	Alt.	169	CTX: 1 g·m^{-2} day 1
						ADR: 45 mg·m^{-2} day 1
		14–17	NO	Seq	165	E: 100 mg·m^{-2} day 1–3
JOHNSON [23]	30 Gy/10 F	1–2	Yes	Early	156	CTX: 1 g·m^{-2} day 1
						ADR: 40 mg·m^{-2} day 1
				No irr.	230	VCR 1 mg·m^{-2} day 1
MURRAY [20]	40 Gy/15 F	3–5	Yes	Early	155	P: 25 mg·m^{-2} day 1–3+
		15–17	Yes	Late	153	E: 100 mg·m^{-2} day 1–3

Alt.: alternating; Seq: sequential; P: cisplain; E: etoposide; CTX: cyclophosphamide; VCR: vincristine; ADR: doxorubicine; F: Fraction; irr.: irradiation.

based simulation of the chest irradiation may each contribute to the better long-term survival rates seen today.

Timing, dosage and fractionation of the chest irradiation are not new issues in SCLC. Early trials, however, were in general unable to give clear answers. The advantages anticipated were too optimistic so the trials were underdimensioned. Even the meta-analysis [2] was unable to prove significant differences in survival related to early *versus* late radiotherapy or to sequential *versus* nonsequential regimes.

Establishment of nationwide or international joint trials is the key to the recruitment of enough patients. The Canadian Lung Cancer Group is an example to follow and one of the questions investigated by the Canadian group is the role of timing of the chest irradiation in relation to the course of chemotherapy of limited-stage SCLC [20]. A total of 308 patients were randomized to early (week 3) or late (week 15) irradiation concurrent with PE. The two agents were alternated with cyclophosphamide, doxorubicine and vincristine (CAV) for a total of six cycles of chemotherapy. The dose of radiotherapy was 40 Gy in 15 fractions over 3 weeks. Both progression-free and overall survival were significantly superior in the early radiotherapy arm. Thus, overall survival after 2 yrs was 40% *versus* 34% (tables 1 and 2), and after 3 yrs 30% *versus* 22%. The cumulative proportions of local recurrence did not differ, however, exceeding 50% in both arms. In a Danish trial [21] 199 patients were randomized to early (weeks 1, 2, 4 and 5) or late (weeks 19, 20, 24, 25) radiotherapy. A course of PE was given in week 3 and week 22, respectively and altogether the chemotherapy comprised 3 cycles PE+6 cycles CAV. The first cycle of chemotherapy was delayed for 2 weeks in the "early" arm. There was no difference in survival between the arms. The 2-yr survival rates were 20 and 19%, respectively.

The Danish trial delayed chemotherapy in the "early" arm to avoid concurrent treatment. PE can, however, safely be given concurrently with radiotherapy, in contrast to the anthracyclines, which significantly increases the normal tissue radiotoxicity. This problem was clearly revealed in a North American multicentre trial [24] randomizing 386 patients to receive six-series CAV, given on day 1, every 3 weeks with or without concurrent chest irradiation: 30 Gy in 10 fractions weeks 1 and 2, plus 15 Gy in five fractions in week 7. Irradiation plus CAV increased the treatment toxicity, especially the haematological: 60% of the patients had grade 4 neutropenia compared to 39% in the other arm. There were six treatment-related deaths compared to three in the chemotherapy-alone arm. Only 57% of the patients received at least 80% of the intended dosage of the two myelotoxic agents (C and A) compared to 79% of the patients in the chemotherapy-alone arm. There was no significant difference in overall survival between the two arms but 2-yr survival in irradiated patients was 33% compared to 24% in nonirradiated patients.

The question of early *versus* late and of alternating

Table 2. – Conventional thoracic radiotherapy regimes (continued)

First author [ref. no.]	Arm	Median survival months	Log rank test	2-yr survival %	5-yr survival %	Leukopenia ⩾grade 4 %	Neutropenia ⩾grade 4 %	Oesophagitis ⩾grade 3
WORK [21]	Early	11	NS	20	11	23		
	Late	12		19	12	6		
GREGOR [22]	Alt.	14	NS	26			72	3
	Seq.	15		23			42	3
JOHNSON [23]	Irr	14	NS	33	16		60	13
	No irr.	13		24	12		39	1
MURRAY [20]	Early	21	p=0.008	40	20		70	15
	Late	16		34	11		61	8

NS: not significant; irr.: irradiation; Alt: alternating; Seq: sequention.

Table 3. – Trials on twice-daily thoracic irradiation

First author [ref. no.]	Radiation	Schedule week	Concurrent	Arm	Patients n	Chemotherapy regime
JEREMIC [25]	54 Gy/36 F	1–4	Yes	Early	52	Carbo: 30 mg·m^{-2}
	54 Gy/36 F	6–9	Yes	Late	51	E: 30 mg·m^{-2} …daily (P: 30 mg·m^{-2} day 1–3 E: 120 mg·m^{-2} day 1–3) ×4
TURRISI [3]	45 Gy/25 F	1–5	Yes	ODR	206	P: 60 mg·m^{-2} day 1
	45 Gy/30 F	1–3	Yes	TDR	211	E: 120 mg·m^{-2} day 1–3
BONNER [26]	50.4 Gy/28 F	1–6	Yes	ODR	132	P: 30 mg·m^{-2} day 1–3
	48 Gy/32 F	1–2 & 5–6	Yes	TDR	130	E: 100 mg·m^{-2} day 1–3
MENNECIER [27]	45 Gy/30 F	4–6	Yes	Phase II	31	P: 75 mg·m^{-2} day 1 E: 120 mg·m^{-2} day 1–3
NISHIWAKI [28]	45 Gy/30 F	day 2–22	Yes	Early	114	Same q. 3 weeks
		day 252–273	No	Late	114	All series prior to the irradiation

ODR: once-daily radiation; TDR: twice-daily radiation; Carbo: carboplatin; P: cisplatin; E: etoposide.

versus sequential chest irradiation was addressed in a European multicentre trial (EORTC) randomizing 335 patients to early alternating or late sequential thoracic irradiation. The chemotherapy: five courses cyclophosphamide, doxorubicine, and etoposide (CAE) was not given concurrently. In the early arm, 50 Gy was given in weeks 6, 10, 14 and 18 alternating with CAE while patients in the late arm received 50 Gy at weeks 14–17, *i.e.* sequentially given between two courses of CAE. The dosage of chemotherapy was the same in the two arms, and >95% of the scheduled doses could be given in both, but with a cyclus time of 3 weeks in the sequential arm, and 4 weeks in the alternating arm, the dose rate (mg·m^{-2}·week^{-1}) differed with as much as 31%. The relative risk of death was in favour of patients treated with the sequential regime (0.88) but the difference was not statistically significant. Grade 4 leukopenia occurred in 72% of patients in the alternating arm compared to 42% in the sequential arm.

Hyperfractionation may increase the efficacy of radiotherapy in SCLC. The theory is based on *in vitro* irradiation of SCLC cells, which do not exhibit the characteristic shoulder phenomenon reflecting repair of sublethal damage. Twice-daily radiotherapy (TDR) in weeks 2, 5 and 8 alternating with chemotherapy (PE) was investigated in an early pilot study [23] but the outcome did not differ remarkably from usual-treatment outcome at that centre neither in efficacy or toxicity. But a much larger, randomized intergroup trial [3] resulted in significantly higher survival rates in the TDR arm compared to the once-daily radiotherapy (ODR) arm. Chemotherapy: four series PE was given concurrently in both arms. The total dose of radiotherapy was 45 Gy in both regimes (tables 3 and 4). Kaplan-Meier curves of overall survival were superimposable the first year but then began to deviate, resulting in differences of 47% *versus* 41% after 2 yrs and 26% *versus* 16% after 5 yrs. The toxicity was similar in the two arms: grade 4 granulocytopenia in 60% and 59% of the patients, respectively, and grade 4 thrombocytopenia in 8% in both arms. Grade 3 oesophagitis was seen in 27 and 11%, respectively, reflecting that 45 Gy in TDR *versus* ODR are not biologically equivalent regimes. For comparison, in a trial [24] of CAV plus concurrent irradiation, 30 Gy in 10 fractions, the haematological toxicity was similar and grade 3 oesophagitis occurred in 13%, but rates of long-term survival were considerably lower.

The oesophageal mucosa is early reacting normal tissue and acute oesophagitis (⩾grade 4) is a major clinical problem when chemo- and radiotherapy are given concurrently. The dose-limiting toxicity of TDR concurrent with cisplatin, cyclophosphamide and etoposide in conventional doses was investigated by CHOI *et al.* [29] in a phase I study. The maximum-tolerated dose (MTD) of TDR was 45 Gy in 30 fractions over 3 weeks compared to at least 70 Gy in 35 fractions over 7 weeks for daily radiotherapy.

Table 4. – Trials on twice-daily thoracic irradiation (continued)

First author [ref. no.]	Arm	Median survival months	Log rank test	2-yr survival %	5-yr survival %	Leukopenia ⩾grade 4 %	Neutropenia ⩾grade 4 %	Oesophagitis ⩾grade 3
JEREMIC [25]	Early	34	p=0.052	71	30	12		29
	Late	26		53	15	12		25
TURRISI [3]	ODR	19	p=0.04	41	16	39	60	16
	TDR	23		47	26	44	59	32
BONNER [26]	ODR	22	NS	47		38		5
	TDR	20		41		36		12
MENNECIER [27]	Phase II	14		25		58[#]		50
NISHIWAKI [28]	Early	27	p=0.057		24			
	Late	20			18			

NS: not significant; ODR: once-daily radiation; TDR: twice-daily radiation. [#]: grade 3 and 4.

Doses above this MTD seem to be applicable, however, if chemotherapy doses are reduced.

Other policies of TDR: early *versus* late and early concurrent *versus* late sequential, were investigated in two randomized trials, a Yugoslavian-Japanese [25] and a Japanese [28], respectively. In the first trial 54 Gy TDR in 36 fractions was given early: week 1–4; or late: week 6–9, concurrently with carboplatin (30 mg·day^{-1}) plus etoposide (30 mg·day^{-1}). Grade 3–4 acute oesophagitis was observed in 29% of 52 patients and in 25% of 51 patients, respectively. Subsequently, the patients received four-series PE in conventional doses. Median survival was >2 yrs in both arms, and the 5-yr survival rates were 30 and 15%, respectively, favouring the early radiotherapy regime. The other trial [28] included 231 patients between 1991–1995. Patients in both arms received TDR 45 Gy in 3 weeks, initiated on day 2, concurrent with PE in arm C and after four-series PE in the sequential arm S. A total of four-series PE was given, every 4 weeks in arm C but three-weekly in arm S. Dosage was the same. Median survival was 27 and 20 months, respectively, and 5-yr survival rates were 24 and 18% (p=0.057). Myelotoxicity was more severe in arm C but the nonhaematological toxicity, including oesophagitis, was not significantly different between the two arms. In contrast to these promising data experience in a French trial [27] on TDR was more sinister. The 27 patients received 45 Gy in 30 fractions concurrently with the second of six series PE (tables 3 and 4). The 2-yr survival rate was only 25% and the toxicity was problematic. Thus, 18 patients (67%) had grade 3–4 neutropenia, and two died whilst febrile and neutropenic and grade 3–4 oesophagitis was observed in 50% of the patients.

In a North-American randomized trial [26] TDR was given in split-course: 16 fractions on days 1–10 plus 16 fractions on day 29–38 to a total of 48 Gy was not superior to once-daily irradiation of 50.4 Gy in 28 fractions over 6 weeks. The 2- and 3-yr survival rates were 47 and 34% for patients in the ODR arm and 45 and 29% for patients in the TDR arm (p=0.44). The toxicity level was acceptable and similar in the two arms except that there were significantly more patients with oesophagitis in the twice-daily arm: 12 *versus* 5%.

It may be concluded that TDR plus concurrent chemotherapy seems to be the best treatment for limited-stage SCLC leading to 5-yr survival in one-quarter of the patients. The regimen is, however, quite toxic for some patients. Optional patients are patients in the good-risk group characterized by a median survival of 20 months and a 2-yr survival rate of 40%. Staging procedures and other inclusion criteria applied in North American trials seem more appropriate for selection of this patient category than those used in European trials. And selection is important in order to reduce overtreatment and toxic complications in patients who, it must be anticipated, basically have poor chances of long-term survival. Still, the strategy of early radiotherapy in a twice-daily fractionation, concurrent with PE, needs further documentation in confirmatory trials. At the same time clinical investigations are needed to find a good treatment for limited-stage patients in whom the concurrent chemo- plus TDR is too toxic. Seen in a broader clinical perspective that is also a challenge.

Prophylactic cranial irradiation

Brain metastases presenting at time of diagnosis can be brought into remission with systemic chemotherapy [30] but systemic chemotherapy cannot prevent occurrence of brain metastases. About 20–30% of the patients develop brain metastases during therapy [31]. Patients in complete remission at conclusion of chemotherapy, proved with restaging procedures including a brain CT scan, have a cumulative risk of 50–60% of developing brain metastases over the subsequent 2 yrs. Survival after occurrence of brain metastases is short: median 3–6 months, although long-term survival can be seen in patients, who remain in systemic remission [32]. The rate of brain metastases occurring in complete responders after conclusion of chemotherapy can be reduced significantly if cranial irradiation: 24–36 Gy is given prophylacticly [17, 22, 33] but an observed positive impact on overall survival was not statistically significant in these trials. This problem was solved with a meta-analysis published in 1999 [5]. Survival and relapse data on 987 patients from seven randomized trials were analysed. A total of 526 patients had PCI while 461 were controls. All were in complete remission at time of randomization. A minority of 140 patients (14%) had extensive disease when the systemic chemotherapy was initiated. The cumulative incidence of brain metastases 3-yrs after randomization was 33% in the PCI group compared to 59% in the control group. The risk of death was reduced 16% (p<0.01) in the PCI group corresponding to an increase in the 3-yr survival rate from 15.3 to 20.7%. The survival benefit appeared after 1 yr and the difference between the Kaplan-Meier curves persisted beyond 6 yrs. An editorial in the same issue of the *New England Journal of Medicine* concluded that "it is now resonable to include prophylactic irradiation as part of the treatment in patients with limited small-cell lung cancer … and of patients with extensive disease who have isolated metastases and are in complete remission" [34]. The patient's age had no influence on the outcome. An irradiation dose of 30–40 Gy led to a significant lower risk of brain metastases compared to 24–25 Gy but the difference in overall survival (death hazard 0.81 *versus* 0.88) was not significant. A European multicentre randomized trial has now been initiated to investigate if 30–40 Gy is better than the lower dose. With a statistical power of 75% and α=0.05 a total of 374 patients must be included in each arm. The outcomes of the meta-analysis have been reproduced in two new meta-analyses [35, 36]. MEERT *et al.* [35] were concerned about the paucity of data on possible late neurological impairment following PCI. Currently, the worried patient can be reassured that late toxicity after PCI, such as impairment of cognitive function, is less frequent than suggested after observations made with an early generation CT scanner [37]. Three investigations [17, 22, 38] found few additional patients with abnormal

neurological or neuropsychological findings as well as CT-scan changes 2 yrs after PCI compared to baseline examinations performed after chemotherapy and before randomization to PCI. At baseline, however, impairments of cognitive functions could be detected in up to 50% of the patients while only a few had CT abnormalities, *e.g.* 17% of 183 patients in the French study [17]. New CT abnormalities occurred in 10% of the patients after PCI *versus* 3% in the control group (p=0.6). For the individual patient, of course, loss of function may be a great problem, and possible risk factors should therefore be clarified, such as age and previous vascular incidents. PCI should not be given concurrently with the systemic chemotherapy.

High-dose chemotherapy

Two decades after the first trials were initiated [39, 40] high-dose chemotherapy with stem-cell support is still an experimental treatment strategy in SCLC. It has not been possible to prove a clear dose-effect relationship in chemotherapy of SCLC [41], the number of patients included in high-dose trials are restricted, because the age and general physical condition of the patients with SCLC will often make high-dose chemotherapy with stem-cell support a risky policy. No large randomized trials have been performed and the data available are not especially promising [42–46] (table 5). Patients with extensive-stage disease do not seem able to obtain longer relapse-free survival than obtained on conventional treatment regimes and rates of long-term survival in limited-stage patients do not differ remarkably from the rates obtained with four-series of PE plus twice-daily chest irradiation [3].

Granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor and dose intensity. G-CSF has well defined roles in high-dose chemotherapy where it is used for mobilization of peripheral blood stem cells (PBSC) and for stimulation of granulocyte regrowth after retransfusion of PBSC. It′s potential role as a way of increasing dosage of chemotherapy and thereby efficacy without use of PBSC support has been investigated in a number of trials. Two almost identical randomized trials [47, 48] included a total of 341 SCLC patients (27–39% with limited-stage disease) who received a relatively aggressive combination of cyclophosphamide 1 $g \cdot m^{-1}$, doxorubicine 50 $mg \cdot m^{-1}$, and etoposide 120 $mg \cdot m^{-1}$ on days 1–3 plus or minus subcutaneous treatment with G-CSF on days 8–13. Neutropenia with fever occurred in 28 and 57% in the arms of a trial by CRAWFORD *et al.* [47] and in 26 and 53% in a trial by TRILLET-LENOIR [48], and the number of hospitalization days were significantly reduced in both studies. Response and survival rates, however, were not statistically different. The question of cost was not considered in these papers but NICHOLS *et al.* [49] made an effort to calculate the cost consequences of a clinical strategy including G-CSF. They reviewed a sample of unselected patients treated with standard-dose chemotherapy in the period 1987–1992. The incidence of neutropenic fever was 12% in the first cycle and 18% overall. Assumptions of the effectiveness of G-CSF were based on data from the Neupogen licensing trial. A policy of 25% dose reduction alone after episodes of neutropenic fever was cheapest, addition of G-CSF in chemotherapy cycles after an episode increased cost moderately with a factor of 1.4 while pre-emptive use of G-CSF with all courses of chemotherapy would increase cost with a factor 6.7 to a total of 1.29 million dollars·$patient^{-1}$. A cost-effective and ethically appropriate policy could make use of a less-aggressive regime to patients with a risk of neutropenic fever in the first cycle of >25%, estimated from simple characteristics as age, LDH, stage of disease and performance status [50, 51].

In addition to G-CSF, GM-CSF can reduce white blood cell (WBC) nadir after chemotherapy. The feasibility and possible advantage of GM-CSF after concurrent chemo- and radiotherapy in limited stage SCLC was investigated in a randomized trial by the Southwest Oncology Group [52] (table 6). Treatment was a combination of cisplatin 25 $mg \cdot m^{-1}$ on days 1–3 plus etoposide 60 $mg \cdot m^{-1}$ on days 1–3, and chest irradiation: 45 Gy during week 1–5. There were significantly more patients with life-threatening thrombocytopenia in the GM-CSF arm, more days in hospital, more who needed intravenous antibiotics, more with nonhaematological toxicity, and more toxic deaths. There was no significant difference in survival and both 2-yr and 4-yr survival rates were inferior in the GM-CSF arm as compared to the control arm. It was concluded that concurrent use of haematological growth factors plus chemotherapy and daily radiotherapy should be avoided.

The feasibility and efficacy of dose-intensification plus GM-CSF in extensive SCLC was investigated in a joint French trial [53] (table 6). Same cumulative doses of etoposide, cyclophosphamide, epirubicine and cisplatin were given in four cycles in the GM-CSF arm and in six cycles in the control arm. Cyclus time was 28 days and GM-CSF was given on days 10–14. The actual median cumulative doses received were: 84% in the control arm *versus* 77% in the high-dose arm. There were five and eight toxicity-related deaths in the control arm and the GM-CSF arm, respectively. Grade 4 neutro- and thrombocytopenia within the first two cycles as well as survival data are summarized in table 6. The trial was stopped at the first planned interims analysis when it was realized that GM-CSF did not enable dosage acceleration. It was concluded that the higher dose-intensity achievable with this regimen in the treatment of extensive stage SCLC had no positive impact on the treatment outcome.

Similarly, outcome was also negative in a joint European trial on increased dose-intensity plus GM-CSF in limited-stage SCLC [54]. In a two-by-two factorial design patients were firstly randomized to vincristine, iphosphamide, carbaplatin, etoposide (VICE) chemotherapy every 3 weeks or every 4 weeks and secondly randomized to treatment with GM-CSF or not for 14 days in each cycle (table 6). Radiotherapy was first delivered after completion of the planned six-cycles of chemotherapy. GM-CSF did not reduce the incidence of haematological complications

Table 5. – Trials on high dose chemotherapy plus haematological stem cell support

First author [ref. no.]	Study period	Patients n	Ext. stage	Induction regime	High-dose regime	Radiotherapy	Survial		
							Median months	2-yr %	5-yr %
BRUGGER [42]	1992–1994	18	0	IFX 4 g·m^{-2} P 50 mg·m^{-2} E 500 mg·m^{-2} EPI 50 mg·m^{-2} (Wk 1 & 3)	IFX 4 g·m^{-2} Carbo 250 mg·m^{-2} E 500 mg·m^{-2} EPI 50 mg·m^{-2} days 1–3 wk 7 +PBSC+G-CSF	Chest: 50 Gy PCI: 30 Gy		78	
ELIAS [43]	1985–1994	36	0	No standard 4 series given in referring dept.	CTX 1875 mg·m^{-2} P 55 mg·m^{-2} BCNU 160 mg·m^{-2} days 1–3 +marrow/PBSC (+G-CSF)	Chest: 50–56 Gy PCI: 30 Gy		53	41
VAN DE VELDE [44]	1993–1996	39	0	IFX 3–4 g·m^{-2} days 1–3 EPI 30–40 days 1–3 (Wk 3)	E 120–150 mg·m^{-2} days 1–3 Carbo AUC 5 days 1–2 Wks 1, 3, 6 & 9 IFX+EPI, wk 6 E+Carbo, wk 9 PBSC day 5 wk 3, 6, 9+G-CSF	Chest: 2 Gy×5	24.6	51	18
LEYVRAZ [45]	1994–1997	69	39	EPI 75 mg·m^{-2} days 1–2	IFX 2.5 mg·m^{-2} Carbo 300 mg·m^{-2} E 300 mg·m^{-2} Days 1–4 wk 3, 7, 11 PBS+G-CSF	Chest: 37 pts No standard PCI: 24 pts No standard	13.5 LIM: 18 EXT: 11	32 5	18 0
BESSHO [46]	1995–1997	11	5	EXT: P 60 mg·m^{-2} days 1+8 Irinp 50 mg·m^{-2} days 1+8 ×3–4 q. 3–4 wks LIM: P 50 mg·m^{-2} days 1+8 E 80 mg·m^{-2} days 1, 2, 8, 9 Wk 1–3	IFX 3 g·m^{-2} days 1–4 Carbo 400 mg·m^{-2} days 1, 3, 5 E 500 mg·m^{-2} days 1, 3, 5	 Chest: 1.5 Gy×30 twice daily	15, 17, 18 and >35 >19, >21, >22, >23		

IFX: ifosphamide; CTX: cyclophosphamide; EPI: epirubicine; Carbo: carboplatin; P: cisplatin; E: etoposide; PBSC: peripheral blood stem cells; G-CSF: granulocyte colony stimulating factor; LIM: limited disease; PCI: prophylactic cranial irradiation.

Table 6. – Impact of granulocyte macrophage colony stimulating factor and dose intensity in treatment of small cell lung cancer

First author [ref. no.]	Study period	Patients n		Arm	Ext. stage %	Regime	Survival		Toxicity		CR rate %
							Median months	2 yr %	gr 4 neutr- %	thr. penia %	
BUNN [52]	1989–1991	215	108	C	0	E 60 mg·m^{-2} days 1–3	C: 17	35	24	6	44
			107	GM	0	P 25 mg·m^{-2} days 1–3	GM: 14	25	18	35	36
						3 wk ×6					
						Chest irr: 45 Gy wk 1–5					
PUJOL [53]	1991–1994	125	60	C	100	E 75/110 mg·m^{-2} days 1–3	C: 11	15	92	32	20
			65	GM	100	P 100/120 mg·m^{-2} day 2	GM: 9	5	100	78	28
						CTX 400/600 mg·m^{-2} days 1–3					
						EPI 40/60 mg·m^{-2} day 1					
						4 wk ×6/×4					
STEWARD [54]	1992–1993	300	153	S	0	VCR 0.5 mg·m^{-2} day 15	S: 12	18			63
			147	I	0	IFX 5 g·m^{-2} day 1	I: 15	33			57
						Carbo 300 mg·m^{-2} day 1					
						E 120 mg·m^{-2} days					
						1–2 240 mg·m^{-2} day 3					
						S: q. 4 wk I: q. 3 wk ×6					
						Chest irr & PCI: After chemo.					
						No standard regime.					

C: control; GM: GM-CSF; S: standard; I: intensified; VCR: vincristine; CR: complete remission; IFX: ifosphamide; CTX: cyclophosphamide; EPI: epirubicine; Carbo: carboplatin; P: cisplatin; E: etoposide; nevtr-: neutropenia.

and it had no significant impact on either response rates or survival. Chemotherapy every 3 weeks prolonged survival in both limited and extensive-stage disease, and this influence was significant in a Cox analysis also including stage and tumour size. GM-CSF, however, had no influence on the ability to maintain the higher-dose intensity.

G-CSF has been investigated in similar randomized trials investigating accelerated chemotherapy plus or minus G-CSF (table 7). WOLL *et al.* [55] used the VICE regimen and a policy where next cycle was delivered as soon as the WBC count was $\geqslant$3.0, *i.e.* there was no fixed-dose interval. Dose-intensity was high in both groups and significantly higher in the G-CSF arm, leading to more treatment-related deaths: six *versus* one. The 2-yr survival rate was best in the

Table 7. – Impact of granulocyte colony stimulating factor and dose intensity in treatment of small cell lung cancer

First author [ref. no.]	Study period	Patients n	Arm	Extensive stage %	Regime	Survival		Toxicity	
						Median months	2 yr %	$\geqslant$2 neutr- %	thr. penia %
WOLL [55]	1990–1991	65	C	31 (10)	VCR 1 mg·m^{-2} day 1	C: 16	15		
			G	34 (6)	IFX 5 g·m^{-2} day 1	GM: 17	32		
					Carbo 300 mg·m^{-2} day 1–3				
					E 120 mg·m^{-2} day 1–2				
					240 mg·m^{-2} day 3				
					S: q. 2–3 wk ×6				
					Chest irr: 12.5 Gy ×1				
					PCI: 8 Gy ×1				
FURUSE [56]	1998	227	C	113 (100)	CAV/EP	C: 10.9	9	83	26
			G	114 (100)	CODE:	G: 11.6	12	83	73
					P25 mg·m^{-2} weekly				
					VCR 1 mg·m^{-2} week 1, 2, 4, 6				
					ADR 40 mg·m^{-2} +				
					E 80 mg·m^{-2} week 1, 3, 5, 7, 9				
THATCHER [57]	1993–1996	403	S	202 (23)	ADR 40 mg·m^{-2} day 1	S: 11	8	83	25
			I	201 (22)	CTX 1 g·m^{-2} day 1	I: 12	13	21	36
					E 120 mg·m^{-2} day 1				
					240 mg·m^{-2} day 2–3				
					S: q. 3 wk I: q. 2 wks				
					Chest irr: After chemo.				
					No standard regime				

IFX: ifosphamide; CTX: cyclophosphamide; ADR: doxorubicine; Carbo: carboplatin; P: cisplatin; E: etoposide; PCI: prophylactic cranial irradiation; S: standard; I: intensified; neutr: neutropenia; VCR: vincristine.

G-CSF arm: 32% *versus* 15%, but the survival difference was not statistically significant. The same outcome of a similar strategy was observed in a Japanese randomized trial on 227 extensive disease patients [56]. Patients in the control arm received CAV alternating with EP in conventional dosage *versus* weekly cisplatin, oncovine, doxorubisine, etoposide (CODE) plus G-CSF in the investigative arm G (table 6) (C: cisplatin 25 $mg \cdot m^{-2}$ weekly, O: vincristine 1 $mg \cdot m^{-2}$ in weeks 1, 2, 4, 6 DE: doxorubicin 40 $mg \cdot m^{-2}$+etoposide 80 $mg \cdot m^{-2}$ for 3 days in weeks 1, 3, 5, 7, 9). Dose-intensity in arm G was twice that in the control arm, four *versus* 0 toxic deaths were observed, the response rates were 84 *versus* 77% but no significant difference in survival was achieved: median survival being 11.6 months and 10.9 months. A slightly different strategy was applied in a large British trial (THATCHER *et al.* [57]). Patients were randomized to receive (ACE) adriamycin 40 $mg \cdot m^{-2}$, cyclophosphamide 1,000 $mg \cdot m^{-2}$ and etoposide 100 $mg \cdot m^{-2}$ *i.v.* on days 1 and 240 $mg \cdot m^{-2}$ *p.o.* on days 2 and 3 every 3 weeks (control arm) or ACE every 2 weeks plus G-CSF subcutaneous for 14 days after each treatment. Patients in the accelerated arm survived longer, corresponding to a reduced hazard ratio of 0.80. The hazard reduction was the same in both limited- and extensive-stage disease. The Kaplan-Meier curves deviated beyond 12 months with 2 yr survival rates of 13 and 8%, respectively. Grade 3–4 neutropenia was much less frequent in the G-CSF arm (table 7) but more blood transfusions were given. The use of G-CSF added significantly to the cost of the therapy and it is necessary to find a more cost-effective way of using G-CSF. The trial showed, that dose intensification is possible, and that it seems to have a positive impact on the treatment outcome, encouraging further trials on the strategy.

Extensive disease

Treatment outcome in extensive-stage SCLC is a sinister story. Various strategies have been investigated but progress has been minimal. With the introduction of etoposide and cisplatin in the late 1970s a new, active combination was available, partly noncross resistant to the CAV regime. A computer model by GOLDIE and COLDMAN [58] predicting superiority of alternating compared to sequential treatment with noncross resistant regimes, could thus be tested in clinical practice. The model was corroborated by a Canadian trial on 289 patients [14]; while others were unable to prove statistically significant differences in survival, including a 3-armed intergroup trial on 437 patients [59]. The principle does not add to either cost nor toxicity and it is still frequently applied in extensive disease.

CHUTE *et al.* [60] have made an interesting retrospective analysis of survival characteristics in extensive SCLC in North America in the last 20 yrs as reflected in data from the control arms of phase III trials and from cases registered in the Surveillance, Epidemiology, and End Results (SEER) database. Both data sources reflected an improvement in median as well as 5-yr survival when data from 1972–1981 were compared with data from 1982–1990. Median survival in trials increased from 7.0 to 8.9 months and from 6.5 to 8.2 months in the SEER database. The 5-yr survival rate rose from 0.8% to 1.6%. Least square regression analysis of data from the trials showed that treatment with cisplatin and year of study initiation were both significantly related to median survival time. The influence of "year of study initiation" could be caused by stage migration [61] but the SEER data suggested a prolongation for all SCLC patients over the period. Prolongation of survival in SCLC with time could, in addition to better combinations of cytotoxic agents, be a result of improved means of general medical management including specific supportive care.

The retrospective analysis cannot, however, point out especially beneficial treatment strategies for extensive SCLC. The clinical characteristics of these patients vary much more than in patients with limited disease; some only have a minor lesion such as a lymph node high on the neck while others have multiple metastases in several organs. Aiming to find a main thread AISNER [62] reviewed trials on extensive-stage SCLC from the 1990s. It was found that it was useful to categorize treatment strategies into one of three groups: The aggressive therapeutic approach (29 series), the intermediate regimes (10 series) and the minimal approach (for poor-prognosis and for elderly patients) (10 series). Complete remission (CR) rates were higher and median survival times longer in the aggressive category compared to those in the intermediate category, while data on other important endpoints such as rates of early death and long-term survival and, not least, on quality of life (QoL) were rarely available. The "minimal" approach resulted in response and survival rates considerably below the figures in the other two groups. How were patients selected to treatment in one or the other category? Aggressive treatment is not for poor-risk patients. But what about the poor-risk patients? Is it clinically meaningful and ethically correct to operate with a minimal approach? Many in this category die early, because treatment is insufficient or because they are too sick when treatment is initiated. "An early death from progressive disease is not likely to improve QoL." AISNER states [62], thinking of those who were undertreated, and continue "Whether the toxicity-to-benefit ratio is appropriate to an individual patient is therefore a matter to be discussed between the patient and his or her care provider." This is a point, but AISNER [62] does not refer to a toxicity-to-benefit model which could help the patient and the caretaker with this difficult choice. Simple algorithms can be established, however, predicting risk of early death from pretreatment characteristics such as performance status, serum LDH and age [63]. If performance status (PS)>1 and LDH above the upper normal limit each contribute with one risk point patients can be categorized into one of three risk groups as shown in table 8. The data were retrieved from the Copenhagen database, supplemented with a European series [64] to illustrate the consistency of the "system". With these two simple clinical attributes it is possible to allocate

Table 8. – Early death (≤day 28) and 2-yr survival in extensive stage small cell lung cancer

Group	Early death				2-yr survival		Patients n (pct.)	
	CPH%			EC%	CPH%	EC%	CPH%	EC%
1	4*	2.8[#]	6.3[¶,+]	3	11.5	11	140 (18)	63 (23)
2	6*	6.4[#]	7.4[¶,+]	4	2.6	8	314 (40)	100 (37)
3	28*	25[#]	35[¶,+]	21	2.4	1	328 (42)	108 (40)

Patients (n=782) treated in trials in Copenhagen (CPH) from 1973–1987 and 271 patients treated at other European Centers (EC) (1985–1992). Group 1: LDH normal and PS=0–1[§]; Group 2: LDH increased or PS>1; Group 3: LDH increased and PS>1. *: all age; [#]: age <65 yrs; [¶]: age >65 yrs; [+]: 232 patients (29.7%) were ⩾65 yrs; [§]: performance status in [64] was scored in Karnoffsly's scale. PS<80 was used as cut-off value.

extensive-stage patients into risk groups with clinically important differences in survival. It is likely that 23% of the patients, who are in the best category, should receive aggressive treatment (and that some may benefit from additional chest irradiation) and that an intermediate treatment approach is optimal for group 2 patients. A meta-analysis on available trial data might answer the question. As for group 3, which includes as many as 40% of the patients, the treatment approach should probably be designed according to physical deficit: one for older patients, and others for patients with compromised lung or liver function, as for patients with a heavily infiltrated bone marrow. Some, desperately ill patients should not be treated at all. Trials aiming to find an appropriate treatment for poor-risk patients are rare.

An example is a feasibility study on per oral etoposide and cyclophosphamide in treatment of poor-prognosis extensive SCLC [65]. Patients who had a low serum albumin or a poor performance status for entry in the current SWOG trial received the two agents for 14 days every 28 days, either once daily (18 patients) or twice daily (39 patients). Age of the patients ranged between 46–94 yrs, 81% had PS=2 (None had PS>2) and 35% had a serum albumin <3.5 $g \cdot dL^{-1}$. Grade 3–4 neutro- and leukopenia were observed in 58 and 53% of the patients, respectively. Early death or progression was observed in 37% of the patients, objective resonse was seen in 26% and unconfirmed response in further 16%. Median failure-free survival was 3–4 months. Serum etoposide on day 2 as well as pretreatment serum LDH were predicitive for the level of granulocyte nadir. Age was not included in the regression analysis. More appropriate regimes should be possible and further trials on this poorest category of the SCLC patients should be initiated.

Aggressive treatment approach for good-risk patients (patients aged <68 yrs and with a PS of 0–2) were investigated by MURRAY *et al.* [66]. The regime: CODE, included weekly cisplatin and doxorubicine plus etoposide every second week. The control regime was CAV alternating with EP, three-times each. The response rate with CODE was higher (87 *versus* 69%) but progression-free and overall survival were not significantly better than in the control group. Death rates from neutropenic fever were 8% in the CODE arm *versus* 1% in the control arm. Ten per cent in both arms were progression free at 2 yrs. Thus, this trial did not support the idea that aggressive treatment is better than a conventional regime in good risk extensive SCLC.

Elderly patients

Elderly patients are, by convention, patients aged ⩾70 yrs. In the 1970s many treatment trials did not include patients >70 yrs but most recent trials include patients aged 70–80 yrs. Compared to the incidence of lung cancer in this age group, however, these patients are underrepresented. This selection reflects a common clinical sense among lung physicians rather than in- and exclusion criteria for the individual trial. Elderly patients will often have cardiovascular disease, diabetes, reduced kidney function, locomotorical handicaps *etc.* making intensive chemo- and radiotherapy inappropriate. Gentle regimes for elderly patients have been investigated but simple guidelines and well-documented treatment options for making an easy choice are still a distant prospect. A retrospective clinical study of DAJCZMAN *et al.* [67] from Quebec, Canada, gives a good impression of the clinical dilemma. Records were reviewed on 312 patients with a pathological diagnosis of SCLC at four McGill University Hospitals from a 7-yrs period: 1985–1991. Elderly patients (⩾70 yrs) comprised 26% of the series, *i.e.* elderly patients were underrepresented as there were 40% in this age group of SCLC patients notified in the British Columbia Cancer Registry in the same period [68]). Staging and treatment of the elderly patients were compared to that of patients aged 60–69 yrs and <60 yrs, respectively. The treatment was regarded to have been "suboptimal" if neither chemo- or radiotherapy had been given to a patient with a performance status of ⩽3. Suboptimal treatment was recorded in 23% of patients aged ⩾70 yrs, compared to 9% of patients aged 60–69 yrs and 5% of patients aged <60 yrs. In limited stage patients chemo- plus radiotherapy was given to 43%, 65% and 69% of patients in the three age groups, respectively. There was no difference in proportions of limited stage disease: 43%, 40% and 45%, but elderly patients were less aggressively investigated compared to younger patients. Only one of 81 elderly patients was enrolled in an experimental protocol compared with 19 and 28% of the younger patient groups. Limited treatment of only 1–3 cycles of chemotherapy was quite frequent in elderly patients: 45% compared to 35% and 22% in the two

younger age groups. Response and survival data in the treated patients reflected these differences in treatment intensity: CR or PR were seen in 25%, 49% and 41% in the three age categories; median survival figures were: 6, 9 and 8.5 months, respectively, but the 2-yr survival rates did not differ accordingly: being 8, 13 and 8%. Optimal *versus* suboptimal treatment was a significant and strong prognostic factor in a Cox analysis while survival was not affected by differences in patient age. These data on treatment outcome may support the view that choice and decisions made by the individual oncologist or lung physician seem to be reasonable. The larger proportions, however, of elderly patients who had few staging examinations, did not receive "optimal" therapy, did not receive chest radiation, only received "limited" chemotherapy, leaves the impression, that treatment outcome in these, selected, elderly patients could have been even better. In other words: a more active approach and uniform handling of elderly patients, including treatment regimens especially designed for this category of patients, are warranted. Ten-years-ago single-agent regimes with etoposide per orally were investigated as candidates for treatment of elderly SCLC patients [69–73]. Given intraveneously in a dosage of 100 $mg \cdot m^{-2}$ for 5 days every 3 weeks BORK *et al.* [71] obtained CR or PR in 65% of the patients, the median survival was 10.6 months and 2-yr survival 8%. Per oral etoposide 200 $mg \cdot m^{-2}$ 5 days every 3 weeks resulted in a similar response rate (62%), but both response duration and median survival were three months shorter. The 2-yr survival was 7% [73]. Two trials comparing *p.o.* etoposide with *i.v.* combination chemotherapy have definitively changed the view on the *p.o.* etoposide regime. The British Medical Research Council conducted a trial on SCLC patients with poor performance (2–4), at any age. Median age was 67 yrs, range: 35–83 yrs. Patients were randomized to receive four-cycles of etoposide 50 mg twice daily for 10 days every 3 weeks or four cycles of a control regimen of intravenous EV or CAV. The trial was closed after inclusion of 339 patients (planned 450 patients) because of inferior results in the etoposide arm. Thus, >30% of the patients in this group died before the 3-month assessment. Median survival was 130 days compared to 183 days in patients treated with intravenous chemotherapy. The palliative effects of the treatments were similar. Same experience was obtained in a trial conducted at four London hospitals [74]. Patients with extensive SCLC, performance status 0–3, were randomized to treatment with six-cycles of either *p.o.* etoposide 100 $mg \cdot m^{-2}$ for 5 days every 3 weeks or *i.v.* PE alternating with CAV. Median age of the patients was 66 yrs (50–86 yrs) and 67 yrs (49–80 yrs), respectively. The trial was stopped after inclusion of 155 patients from a projected intake of 365 patients because of inferior survival outcome in the etoposide arm. Median progression-free survival was only 3.6 months compared to 5.6 months in the control arm, 1-yr survival figures were 9.8% and 19.3%. Although the two trials did not specifically focus on the treatment of elderly patients, the outcome does not support continued use of the regimen in this group either.

A policy of combination chemotherapy regimes specifically designed for elderly patients has been investigated by the Canadian lung cancer group in Vancouver [68, 75]. In the period 1982–1991 elderly or infirm patients with limited SCLC were offered a standard treatment of one-cycle CAV followed 3 weeks later by one-cycle EP plus concurrent thoracic radiotherapy, 20 Gy in 5 fractions or 30 Gy in 10 fractions. Prophylactic cranial irradiation was not routinely administered. The series included 55 patients, 67% of the patients were aged $\geqslant$70 yrs, 55% had PS 0–1, 71% had normal S-LDH, and 60% were females. Although the patients only received two-cycles of chemotherapy and a suboptimal radiotherapy, 28% of the patients survived 2 yrs and 18% 5 yrs.

In the following period: 1991–1994 the Vancouver group replaced the two series CAV with four series PAVE (cisplatin 30 $mg \cdot m^{-2}$ day 1, adriamycin 40 $mg \cdot m^{-2}$ day 1, vincristine 1 $mg \cdot m^{-2}$ day 1, etoposide 100 $mg \cdot m^{-2}$ days 1, 3, 5) plus the same simple irradiation programme for treatment of limited disease and in selected patients with extensive disease. The chest irradiation was given concomitantly with the second cycle of chemotherapy which was then reduced to only PE. A total of 66 patients were treated: 25 patients with limited disease, with a median age of 72 yrs (66–79 yrs), and 41 patients with extensive disease, median age 69 yrs (66–81 yrs). The 2-yr survival rates for limited and extensive stage patients were 38% and 18%, respectively, and the 5-yr survival rates were 24% and 5%. Prognostic attributes such as PS, LDH and metastatic sites did not suggest that these patients were especially selected. It is difficult to explain these favourable results on the basis of the general model of SCLC as a tumour with a high incidence of clonal heterogeneity but from a practical point of view the outcome is very stimulating for further development of specific treatment regimes for elderly patients. Two to four cycles of chemotherapy seem to be appropriate and chest irradiation can be given in less fractions, suggesting, that late lung toxicity does not seem to be a major problem in these patients.

A Japanese phase II trial [76] conducted in 1995–1996, also supports the supposition that a reasonably high initial dose level is important for the outcome. Thus, 36 patients, aged 73 yrs (70–80 yrs), received up to 4 cycles of carboplatin (AUC 5) plus etoposide 100 $mg \cdot m^{-2}$ *i.v.* days 1–3 every 4 weeks. The 44% of patients with limited disease had additional chest irradiation after chemotherapy. Sixty-one per cent of the patients received the scheduled 4 cycles and dose reductions were only necessary in 10% of the patients. Median survival was 10.8 months and 1 and 2-yr survival rates were 47.2% and 15.4%, respectively. Serum LDH, stage and anaemia were significant prognostic factors in a Cox analysis but age was not.

The high rates of long-term survival in these patients could hardly have been obtained without chest irradiation. A subgroup analysis in the meta analysis on thoracic radiotherapy for SCLC [2] proved no benefit of chest irradiation in patients aged $\geqslant$70 yrs, but these data derived from trials using

Table 9. – Phase II treatment trials with new agents

First author [ref. no.]	Agent	Dose mg·m^{-2}	Patients n	RRU %	RRS %	RRR %	Grade 4 neutopenia %
ETTINGER [80]	Paclitaxel	250	36	34			56
KIRSCHLING [81]	Paclitaxel	250	43	35			56
HESKETH [82]	Docetaxel	100	43	25			58
KELLY [79]	Topotecan	125	378	33	15–38	5	50–70
HUBER [83]	Topotecan	1.25	171		14		12
KELLY [79]	Irinotecan	100	50	30–50			NR
CORMIER [84]	Gemcitabine	1000	29	27			18
POSTMUS [85]	Gemcitabine	1000	12		25		NR
MASTERS [86]	Gemcitabine	1000	43			12	26
KELLY [79]	Vinorelbine	25–30	120	27	15		40–60

RRU, RRS, RRR: response rate in untreated relapsing previous sensitive patients and in primarily refractory patients; NR: not reported.

other agents and other radiation schedules such as split course and greater doses on fewer fractions, resulting in greater toxicity than seen today. In current regimes elderly people seem to both tolerate and to benefit from chest irradiation. As an example, the intergroup trial comparing twice-daily with once-daily thoracic radiotherapy [3] patients aged 82 yrs were included. Outcome was independent of age [77] and age was not a risk factor in a multivariable Cox analysis [3]. Treatment in these series also included prophylactic-cranial irradiation to patients in CR and no extraordinary neurotoxicity was observed. Systematic assessments, however, in larger series would be useful. Finally, the populations are changing and the increasing number of elderly people in good general health represents both a stimulus and a demand for development of specific regimes for elderly patients. Many elderly will tolerate combination chemotherapy and all will expect to be offered an individualized, documented and efficacious treatment.

New chemotherapeutic agents

The activity of six new agents have been investigated in phase I, II and III trials during the past 9 yrs but the definitive roles of each agent have not yet been defined [78, 79]. The agents are two taxanes: paclitaxel and docetaxel, two topoisomerase I inhibitors: topotecan and irinotecan, an antimetabolite: gemcitabine and a spindle inhibitor: vinorelbine [80–86] (table 9) (a seventh agent: oxaliplatin, has not yet been tested in SCLC). The phase II trials include previously untreated patients with extensive disease or patients with relapse after >3 months in remission after first-line treatment. A few trials include patients with refractory tumours on first-line treatment. Some trials use G-CSF as rescue or as an integrated part of the treatment. The addition of G-CSF has an influence on the observed haematological toxicity and may have an impact on the response rates. The strategy thus makes it more difficult to compare the outcome with that from other trials.

Comparison of haematological toxiciy data is furthermore difficult because of various ways to describe the observations: nadirs in first cycle or global nadir from all cycles; per cent of patients or per cent of series with grade 3 or grade 4 toxicity. Survival data should be interpreted cautiously because similar pretreatment characteristics of the patients do not prove the same degree of selection.

The taxanes

Two trials investigated the activity of paclitaxel 250 mg·m^{-2} by 24-h infusion [80, 81] (table 9) and achieved response rates as high as 34% and 35%, respectively. The 24-h infusions have since been replaced by 3-h or 1-h infusion times. The high response rates have stimulated several trials with paclitaxel in combination with cisplatin, carboplatin, and etoposide [87–93] (table 10). Investigations on paclitaxel added to the "standard" regimen of cisplatin plus etoposide has naturally had a high priority. Appropriate doses of the three agents have been clarified in a phase I trial in extensive stage patients [90], recommending paclitaxel 175 mg·m^{-2} over a 3-h period, cisplatin 80 mg·m^{-2} and etoposide 80 mg·m^{-2} *i.v.* on day 1 and 160 mg·m^{-2} *p.o.* on days 2–3. G-CSF was only used according to the American Society of Clinical Oncologists' guidelines. The regimen was subsequently investigated by SWOG in a phase II trial on 90 patients with extensive disease [91]. A median survival of 11 months seems encouraging and 7% toxic deaths and nearly 40% with grade 4 neutropenia is not considered extraordinary for a series of patients with extensive SCLC.

GLISSON *et al.* [89] gave paclitaxel 130 mg·m^{-2} over 3 h, cisplatin 75 mg·m^{-2} on day 1, and etoposide 80 mg·m^{-2} *i.v.* on days 1–3 in a trial on 41 patients. Two early septic deaths were observed and grade 4 neutropenia was observed in 44% of 188 courses. The response rate was 90%. A Greek randomized trial [92] including 45% patients with limited disease was stopped prematurely after inclusion of 133 patients because of eight toxic deaths in the three-agents arm compared to none among patients treated with cisplatin and etoposide alone. Same doses as in the SWOG trial were used, G-CSF was used prophylacticly. There was no significant difference in survival between the arms. Grade 4 neutropenia occurred in

Table 10. – Phase II/III trials with taxanes

First author [ref. no.]	Agents	Patients n	Dose of taxan mg·m^{-2}	RRU %	Stage	Grade 3–4 neutropenia %
NAIR [87]	Paclitaxel+Cisplatin	21	135, 3 h	71	E	0
		44	175, 3 h	89	E	2
GROEN [88]	Paclitaxel+Carboplatin	35	175, 3 h	74	L & E	27
GLISSON [89]	Paclitaxel+Cisplatin+Etoposide	41	130, 3 h	90	E	47
KELLY [90]		28	175, 3 h	83	E	82
KELLY [91]		90	175, 3 h	56	E	35
MAVROUDIS [92]		62	175, 3 h	50	L & E	44
BIRCH [93]	Paclitaxel+Carboplatin+Etoposide	84	200, 3 h	89	L & E	NR
FERRI [94]	Docetaxel+Doxorubicine	20	NR	10	E	17
MORENO [95]	Docetaxel+Cisplatin	30	75	62	E	60

RRU: response rate in untreated patients; E: extensive stage; L: limited stage; NR: not reported.

39% of the patients, *i.e.* as in the phase I and II trials. The toxicity problem must thus be taken serious. Poor-risk patients should be excluded and conservative dose reduction rules may be a safer policy than giving G-CSF on demand.

Carboplatin plus etoposide with or without paclitaxel (4 cycles) is under investigation in a randomized trial now including 170 patients (BIRCH *et al.* [93]). Patients with limited disease (53%) receive concurrent chest radiation with cycles 3 and 4. No extraordinary toxicity is mentioned. The response rates in the paclitaxel arm are modestly higher and there is a trend toward improved survival in patients with extensive disease.

Many trials with paclitaxel are still ongoing and it is too early to assess the role of this agent. Other schedules of paclitaxel are under investigation [79], *e.g.* day 10 after cisplatin, as a 24-h infusion on day 5 after topotecan on days 1–5, day 10 after etoposide twice daily days 1–10, or followed by oral etoposide days 2–8. Currently no specific use of paclitaxel in the treatment of SCLC can be advocated, and it is still too early to guess which role paclitaxel will come to play in the treatment of SCLC.

Docetaxel has been much less investigated and the outcome data is not especially promising. A phase II trial on 43 previously untreated patients with extensive disease [82] resulted in a response rate of only 23%. The dose was 100 mg·m^{-2} every 3 weeks. Docetaxel plus doxorubicin in extensive SCLC were investigated in a phase II trial which was discontinued after inclusion of 20 patients because only two patients achieved a PR [94] (table 10). A much better outcome was obtained when combined with cisplatin [95] and it is still too early to preclude activity of docetaxel in treatment of SCLC.

The topoisomerase I inhibitors

The topoisomerase II inhibitor etoposide is fundamental in the treatment of SCLC and another key role is expected for one or both of the two type I inhibitors: topotecan and irinotecan. The sensitivity patterns of the two agents are much alike when tested on cell lines [60] but different from that of etoposide. Both drugs are active in phase II trials on chemo-naïve patients and on patients with previously sensitive tumours [96–100] (table 11). In a phase II trial on 48 chemo-naïve patients with extensive disease [96] topotecan, 2.0 mg·m^{-2} *i.v.* days 1–5 every 3 weeks, resulted in an objective response rate of 39%, median response duration was 4.8 months and median survival 10 months. Prophylactic G-CSF was given to the last 35 patients, reducing occurrence of grade 3–4 haematological toxicity from 92% to 29% of the patients. Currently recommended dose is 1.5 mg·m^{-2} *i.v.* for 5 days every 3 weeks [101]. The agent is well absorbed and the efficacy of tablet treatment is under evaluation in large randomized trials performed by the producer. Single-agent treatment with irinotecan 60 mg·m^{-2} weekly×3 in 4 week cycles results in similar response rates [102] and response rates as high as 84% were seen when the agent was combined with cisplatin

Table 11. – Phase II/III trials with topoisomerase I inhibitors

Reference	Agents	Patients n	Dose of topo-/ irinotecan	RRU %	RRS %	Grade 3–4 neutropenia %
SCHILLER [96]	Topotecan	48*	2.0 mg·m^{-2}	39		92 (29% if +G-CSF)
SORENSEN [97]	Topotecan+Cisplatin+ Carboplatin+Teniposide+VCR	13	0.75–1.25 mg·m^{-2}	90		87
KUDOH [98]	Irinotecan+Cisplatin	75	60 mg·m^{-2} days 1, 8, 15	84		77
MASUDA [99]	Irinotecan+Etoposide	25	70 mg·m^{-2} days 1, 8, 15		71	56
NODA [100]	Irinotecan+Cisplatin	77	60 mg·m^{-2} days 1, 8, 15	89		27
	Etoposide+Cisplatin	77	(100- day 1-3)*,#	67		52

RRU: response rate in untreated patients; RRS: response rate in relapsing previous sensitive patients; VCR: vincristine. *: dose of etoposide; #: 35 patients received granulocyte colony stimulating factor days 6–18.

(60 mg·m^{-2} every 4 weeks) in 75 chemo-naïve patients [98] and 71% when combined with etoposide [99] as second-line treatment. These two combinations are especially interesting: firstly, is a topoisomerase I inhibitor plus cisplatin as efficacious or even better than etoposide plus platinum? And secondly, will alternating (or combined) dosage of a topo I and a topo II agent delay upregulation of topoisomerase 1/2 activity in the tumour cells and thus reduce the risk of treatment resistance?

Question number 1 has already been investigated in a randomized trial on extensive disease comparing irinotecan plus cisplatin (IP) with etoposide plus cisplatin (EP) [100]. The trial was halted at an interims analysis after inclusion of 154 patients because of major difference in survival: the median survival in the IP arm was 420 days compared to 300 days in the EP arm (p=0.0047) and 1-yr survival 60% *versus* 40%. Only 27% of patients receiving IP had grade 3–4 neutropenia compared to 52% in the EP arm. More definitive statements about efficacy of the IP regimen must await conclusion of the trial plus a confirming trial.

Introduction of topoisomerase inhibitors in treatment of limited-stage disease is under way, but there is some anxiety about the toxicity if given concurrently with radiotherapy [103]. Both agents have been investigated in phase I trials on nonsmall cell lung cancer [104, 105]. Severe cases of oesophagitis and pneumonitis were observed in both trials and dose reductions to 33–50% of the otherwise recommended doses seem to be necessary for both agents.

Gemcitabine

Gemcitabine is an antimetabolite and it has a sensitivity pattern which differs from that of other active agents in SCLC. The haematological toxicity of the drug is modest. The agent has proved activity in phase II trials (table 9) but data on its activity in combination regimens is restricted. The Italian "Lazio" group [106] added gemcitabine to the EP regimen in treatment of 43 patients, limited as well as extensive stage disease. The overall response rate was 68% with CR rates of 24% in limited stage and 0% in extensive stage. Dosage of etoposide was only 50 mg·m^{-2} *i.v.* day 3–5 and grade 3–4 neutropenia was seen in only 29% of the cycles reflecting that gemcitabine can be included in a more dose-intensive regime.

Vinorelbine

Vinorelbine is a semisynthetic vinca alkaloid like vincristine and vindesine, which are both active in SCLC. The activity of vinorelbine in phase II trials has been modest (table 9) but response rates of up to 70% have been obtained in combination with cisplatin and etoposide and with carboplatin [79]. The sensitivity profile of the vinca alkaloids and the taxanes are much alike [107] and the clinical activity of vinorelbine in relation to that of vincristine and of paclitaxel should be investigated further in treatment trials.

Concluding remarks

How can these new agents best be integrated in combination regimens for the treatment of SCLC? Are the design of clinical trials sufficiently systematic? Are there too many phase II and too few randomized trials? Should more attention be paid on laboratory data such as sensitivity profiles in cell lines [107] before new combinations of new and old agents are investigated in the clinic? A majority of the trials on the new agents have been supported by the drug companies. Clinicians and drug companies have, in the early phase, a common interest in defining a role for the individual agent. Then ways often part. New agents get ready from the "pipelines", phase I and II trials are requested and it may then be difficult for the clinicians to find time and resources for large, investigator initiated, randomized trials. And randomized trials must be large, typically 250–300 patients in each arm in order to gain sufficient statistical power. To add insult to injury requirements to documentation have been strengthened, it is hardly possible today to have a protocol approved by the scientific ethical committee if it does not fulfil the good clinical practice (GCP) criteria.

It is important to realize and to tell both the public and health authorities that there is not yet a really efficacious standard treatment for SCLC. Patients with SCLC must still be ready to be treated in trials and new (expensive) agents should be restricted to investigative regimes for the sake of continued clinical research and to secure that the lions share of the drug budget goes to development.

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