State of the art in systemic treatment of lung cancer

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Systemic treatment usually means chemotherapy. However, a number of novel non-cytotoxic agents are being investigated for the treatment of this disease; a brief mention of these novel therapies will be made.

Non-small cell lung cancer (NSCLC)

Chemotherapy is standard treatment for patients who have a relatively good performance status (World Health Organization (WHO) 0, 1, and select 2, advanced NSCLC (stage III B and IV)). For many stage III patients, chemotherapy is part of a multi-modality approach, but it is the only modality treatment for those stage IIIB patients with malignant pleural effusion, where radical radiotherapy cannot be administered. A limited number of stage IIIB patients without pleural effusion, for which radiotherapy cannot be given for technical reasons, can also be candidates for chemotherapy. It is important that this distinction is made when defining patients with advanced NSCLC who are candidates for chemotherapy alone, because the entry of many patients with stage III (sometimes even stage IIIA) can appear to improve dramatically the results of phase II and III studies of chemotherapy alone. Chemotherapy improves significantly symptoms and quality of life of patients with advanced NSCLC. A large meta-analysis of randomised trials of chemotherapy versus best supportive care indicated an improvement of approximately 1.5–3 months in median survival [1]. This has been obtained with cisplatin-containing chemotherapy, and this meta-analysis did not define any other agents which, when added to cisplatin, are essential for activity. However, mainly vinca alkaloids (in particular vinblastine and vindesine) or epipodophyllotoxins (mainly etoposide, VP16) have been employed in the studies included in the meta-analysis.

At least 5 relatively novel chemotherapeutic agents have shown activity in advanced NSCLC in the last decade, i.e. gemcitabine, vinorelbine, paclitaxel, docetaxel, and irinotecan. A response rate of about 20% has been obtained in first-line therapy with these agents. For all of these new drugs, some modest improvement in response rate has been obtained in randomised trials, in comparison to cisplatin alone or cisplatin-based standard regimens. For some randomised trials, a significant increase in survival was also shown.

There is presently no standard chemotherapy treatment, but the most commonly employed regimes are: cisplatin–vinorelbine, cisplatin–gemcitabine and carboplatin–paclitaxel. The choice of these regimens is only partially based on results of randomised studies and is often taking into account issues such as safety, side-effects, ease of administration, costs, etc. Table 1 shows the most important randomised studies, published in the past few years, of novel chemotherapeutic agents in combination with cisplatin or carboplatin, against best supportive care, cisplatin alone, or platinum-containing standard regimens, [2–14]. In general, an improvement in response rate was obtained by the majority of the novel regimens, but improvement in survival has been observed less frequently.

Present chemotherapy can induce a median survival of about 9 months in patients with stage IV and stage III with malignant pleural effusion, with a 1-year survival of about 35–40%. Although improving the results of 2-drug combinations in advanced NSCLC appears to be rather difficult, several 3-drug regimens are being tested in randomised studies, and the results are awaited.

It is, however, rather likely that the results of chemotherapy may have reached a plateau, and that it will be rather difficult to obtain better results in advanced NSCLC by chemotherapy alone. Novel treatment modalities are urgently needed in advanced NSCLC. New ways to improve the results of chemotherapy appear to be the use of chemotherapy in combination with novel biological agents. Several of these agents are currently being developed for NSCLC, and results of running randomised studies are eagerly awaited.

Table 1
Recent randomised studies

Regimens	Patients (No.)	Response (%)	MDR (m)	TTP (m)	MST (m)	1-year (%)	Reference
Chemotherapy vs best supportive care (BSC) in advanced NSCLC							
Vin	80	20	NR	NR	28 weeks	32	ELVIS [2]
BSC	81	–	NR	NR	21 ($P = 0.03$)	14	
DXL	137	13	37.1 weeks	12.6 weeks	6.0	25	Raszkowski [3]
BSC	70	–	–	8.9 ($P < 0.001$)	5.7 ($P = 0.026$)	16	
PXL	79	16	NR	4.0	4.8	30	Ranson [4]
BSC	78	–	NR	1.2 ($P = 0.0001$)	6.8 ($P = 0.037$)	28	
MIC	175	32	NR	NR	6.7	25	Cullen [15]
BSC	176	–	NR	NR	4.8 ($P = 0.03$)	17	
Advanced NSCLC with novel agents							
Vin	206	14 ($P < 0.01$)	7.8	NR	31 weeks ($P = 0.01$)	30	LeChevalier [5]
DDP-Vin	206	30	9.2	NR	40	34	
DDP-Vds	200	19 ($P = 0.02$)	9.9	NR	32 ($P = 0.04$)	27	
Vin	119	16	NR	10 weeks	32 weeks	NR	Depierre [6]
DDP-Vin	121	43 ($P = 0.0001$)	NR	20 ($P = 0.0001$)	33	NR	
DDP	209	12	NR	2	6	20	Wozniak [7]
DDP-Vin	206	26 ($P = 0.0002$)	NR	4 ($P = 0.0001$)	8 ($P = 0.0018$)	36	
Gem	72	18	NR	NR	6.6	26	Ten Bokkel [8]
DDP-VP	75	15	NR	NR	7.6	24	
DDP-VP	66	22	NR	4.3	7.2	26	Cardenal [9]
DDP-Gem	69	41 ($P = 0.02$)	NR	6.9 ($P = 0.01$)	8.7	32	
MIC	152	26	8.2	4.8	9.6	34	Crino [10]
DDP-Gem	155	38 ($P = 0.029$)	8.7	5.0	8.6	33	
DDP	262	11	NR	3.7	7.6	28	Sandler [11]
DDP-Gem	260	30 ($P < 0.0001$)	NR	5.6 ($P = 0.0013$)	9.1 ($P = 0.004$)	39	
DDP	223	7	NR	11.6 weeks	27.7 weeks	23	Von Pawel [12]
DDP-Tira	223	20 ($P = 0.001$)	NR	12.9 ($P = 0.0076$)	34.6 ($P = 0.0078$)	34	
DDP-VM	162	28	9.5	4.9	9.9	41	Giaccone [13]
DDP-PXL	155	41 ($P = 0.018$)	8.3	5.4	9.7	43	
DDP-VP	200	12	NR	2.8	7.6	32	Bonomi [14]
DDP-PXL(HD)	201	28 ($P < 0.001$)	NR	5 ($P = 0.007$)	10 ($P = 0.097$)	40	
DDP-PXL(LD)	198	25 ($P = 0.002$)	NR	4.4 ($P = 0.067$)	9.5 ($P = 0.090$)	37	
DDP-Epi	102	32	9	NR	10.5	42	Martoni [19]
DDP-Vin	110	27	8	NR	9.6	39	
MVP	49	14	NR	NR	8.4	NR	Baldini [20]
DDP-IFO-Vin	48	17	NR	NR	8.8	NR	
CRB-Vin	43	14	NR	NR	7.9	NR	

NSCLC = non small cell lung cancer; Ifo = ifosfamide; epi = epirubicin.
MDR = median duration of response; TTP = median time to progression; MST = median survival time; BSC = Best Supportive Care; NR = not-reported; MIC = mitomycin, ifosfamide, cisplatin; DDP = cisplatin; Gem = gemcitabine; Tira = tirapazamine; VM = VM26 (teniposide); DXL = docetaxel; PXL = paclitaxel; Vin = vinorelbine; Vds = vindesine; VP = VP16 (etoposide); HD = high-dose; LD = low-dose P values are for significant differences or borderline significant differences.

Randomised phase II–III trials

Apart from the first randomised studies reported with the combination of cisplatin–vinorelbine by French investigators, the greatest number of randomised studies have been reported during the past two years. Selected results of these studies are summarised in Table 1 [2–14]. However, some studies compared treatment against best supportive care; all of these were positive studies, demonstrating an improvement of survival and some also indicated a better symptom control and quality of life.

Cullen et al. [15] have compared MIC chemotherapy to best supportive care (BSC). MIC was given as follows: mitomycin 6 mg/m^2 and ifosfamide 3 g/m^2 and cisplatin 50 mg/m^2 on day 1, every 3 weeks, up to a maximum of 4 cycles. The response rate was similar to the one reported in several other randomised studies. There was a significantly longer overall survival and this translated into an improved quality of life, assessed using the European Organization for Research and Treatment of Cancer — Quality of Life (EORTC QLQ)-LC13; the quality of life score deteriorated in the BSC arm and sig-

nificantly improved in the MIC arm at 6 weeks, compared to baseline ($P = 0.007$). However, only 109 patients (31%) of patients participated in the QLQ assessment.

A randomised study in elderly patients (70 years or older) with advanced NSCLC has been reported comparing vinorelbine to best supportive care [2]. Vinorelbine was given at 30 mg/m^2 on days 1 and 8, every 3 weeks. Quality of life was assessed with the EORTC QoL instrument. Investigators, blinded to the results, stopped the trial early because of a low enrolment rate. Data from 161 patients of the targeted 350, have been analysed. Vinorelbine-treated patients scored better than control patients on QoL functioning scales, and they reported fewer lung cancer-related symptoms, but reported worse toxicity-related symptoms. Furthermore, there was a statistically significant ($P = 0.03$) survival advantage for patients receiving vinorelbine; median survival increased from 21 to 28 weeks in the vinorelbine-treated group.

A randomised study compared docetaxel alone with best supportive care [3]. Time to progression and survival were significantly in favour of docetaxel. Also, quality of life was better in the docetaxel arm. There was, also, a lower use of analgesics, other tumour-related medications and palliative radiotherapy. However, there was a higher use of antibiotics in the docetaxel arm.

Another randomised study compared paclitaxel versus best-supportive care in 157 advanced NSCLC [4]. Again, in this study chemotherapy was superior to best-supportive care. Quality of life favoured the paclitaxel arm in the functional activity score ($P = 0.043$). The largest difference in survival was observed at 6 months.

In another large randomised study assessing the role of chemotherapy in addition to best supportive care in advanced NSCLC [16], a total of 287 patients were randomised to receive one of two different chemotherapy regimens, or best supportive care. Chemotherapy was either IEP (ifosfamide, epirubicin and cisplatin) or MVP. Both chemotherapy regimens improved survival significantly over best supportive care and quality of life.

Many studies investigated the role of gemcitabine in advanced NSCLC. Crino et al. [10] recently reported a randomised study in 307 patients with untreated advanced NSCLC who were randomised to MIC, a common regimen in use in Europe (mitomycin 6 mg/m^2 and ifosfamide 3 g/m^2 on day 1, and cisplatin 100 mg/m^2 on day 2, every 4 weeks) and a novel regimen of cisplatin and gemcitabine (cisplatin 100 mg/m^2 on day 2, gemcitabine 1 g/m^2 on days 1, 8, 15, every 4 weeks). Although there was a statistically significant greater response rate in the novel regimen ($P = 0.029$), no significant difference was reported in survival, time to progression and quality of life, which was assessed using the EORTC QoL questionnaire with the lung-specific module. Grade 3–4 thrombocytopenia was reported more frequently in the cisplatin–gemcitabine arm (64%) compared to the MIC arm (28%; $P < 0.001$), whereas alopecia was reported more frequently in the MIC arm (39% vs 12%, respectively; $P < 0.001$). Interestingly, the study was sized to detect a difference in quality of life in the first 2 months of treatment in 14 items. This study exemplifies how difficult it can be to report quality of life data and compare them between very different treatments. This study indicates that old fashioned regimens such as the MIC are as good as novel regimens such as cisplatin–gemcitabine, at least as far as survival is concerned.

The Hoosier Group also tested the novel combination of cisplatin–gemcitabine at the same doses as in the Italian study, this time against cisplatin alone given at 100 mg/m^2. Both regimens were given every 4 weeks [11]. A total of 522 patients were randomised in this international study. It proved superiority of the combination against cisplatin alone, in terms of response rate and survival, which reached significance. Toxicity was more frequent, however, in the combination arm: grade 4 neutropenia occurred in 35.3% of patients in the combination arm vs. only 1.2% in the cisplatin alone arm, and grade 4 thrombocytopenia was 25.4% vs 0.8%, respectively. This led to 20.4% of the patients on the combination to receive platelet transfusions vs 0.4% on the cisplatin arm. These differences all appear to be highly statistically significant, but P values were not reported in the article. No other major differences in side-effects were reported. As in the Italian study, less than 50% of patients on the cisplatin–gemcitabine arm received a full dose of gemcitabine, and this was primarily due to haematological toxicity, especially thrombocytopenia on day 15. Only 23% of patients on cycle 6 received full dose gemcitabine, compared to 42% on cycle one, which indicated cumulative haematological toxicity. Seventy-two percent of patients filled in the Functional Assessment of Cancer Therapy – Lung (FACT-L) questionnaire for QoL assessment: in both arms a deterioration of the physical well-being scores was identified to a similar degree, suggesting that this was due to the toxicity of treatments.

Cardenal et al. [9] compared the standard cisplatin–etoposide chemotherapy to the novel combination of cisplatin–gemcitabine in a phase III study that had response rate as the major endpoint. Only

135 patients were entered in this study, which confirmed a higher response rate on the novel combination of gemcitabine 1250 mg/m^2 days 1 and 8 and cisplatin 100 mg/m^2 day 1 every 3 weeks. Also, time to progression was significantly better in the new combination, and a strong trend for improved survival was found ($P = 0.18$). Unfortunately, the study was underpowered to show a difference in survival. The toxicity profile of both combinations was similar, as was quality of life. The evaluation of costs in this study led to the conclusion that direct costs were similar between the two arms [17].

A small randomised study compared gemcitabine given as a single agent at 1 g/m^2 on days 1, 8 and 15 of a 4-weekly cycle, to cisplatin–etoposide [8]. The sample size was set at a level to detect differences in toxicity and tolerability of the two regimens, but was not considered sufficient for a comparison of response rates or survival. Similar response rates and survival were observed in the 2 arms. Gemcitabine had less severe toxicity than the cisplatin-containing arm, and the QoL was relatively better in the gemcitabine arm.

Many studies also investigated vinorelbine in randomised comparisons. Amongst the novel agents, vinorelbine was actually one of the first to be accepted in the USA for the first-line treatment of advanced NSCLC in combination with cisplatin. A large study investigated the combination of cisplatin–vinorelbine compared with the standard combination of cisplatin–vindesine and vinorelbine alone [5]. Forty-five centres included 612 patients in this study. Vinorelbine was administered at a dose of 30 mg/m^2 weekly, cisplatin at 120 mg/m^2 on days 1 and 29 and then every 6 weeks, and vindesine at 3 mg/m^2 weekly for 6 weeks and then every other week. Treatment was continued until progression or toxicity. Only 59% of the patients had metastatic disease in this study. An objective response rate was observed in 30% of patients in the cisplatin–vinorelbine arm versus 19% in the cisplatin–vindesine arm ($P = 0.02$) and 14% in the vinorelbine alone arm ($P < 0.001$). The median durations of survival were 40, 32 and 31 weeks, respectively. Comparison of survival among the three groups demonstrated an advantage for cisplatin–vinorelbine compared with cisplatin–vindesine ($P = 0.04$) and vinorelbine alone ($P = 0.01$). Neutropenia was significantly higher in the cisplatin–vinorelbine group ($P < 0.001$), and neurotoxicity was more frequent with cisplatin–vindesine ($P < 0.004$). A recent update with 6-year follow-up confirmed that survival remained significantly superior ($P < 0.02$ for both arms) [18].

In another study by Depierre et al. 231 eligible patients were to receive either vinorelbine alone, 30 mg/m^2/week, or the combination of vinorelbine, 30 mg/m^2/week and cisplatin, 80 mg/m^2/3 weeks [6]. The two groups differed in terms of objective response rates (16% and 43%, respectively, $P = 0.0001$) and median time to progression (10 vs 20 weeks, $P = 0.0001$). However, the difference was not significant for median survival time (32 weeks, 33 weeks, $P = 0.48$). The addition of cisplatin resulted in an increase in toxicity, in particular renal, haematological, neurological and emetic adverse effects. These toxicities led to treatment discontinuation in 8% and 21% of patients, respectively and 3% and 13% of patients stopped treatment early during objective response (toxicity or refusal). These authors concluded that the cisplatin–vinorelbine combination increased objective response rates and time to progression in comparison with vinorelbine alone, but did not influence the survival of patients. The activity of vinorelbine in the treatment of advanced NSCLC was confirmed. These two French studies clearly show that whereas response rate is a relatively easy endpoint to improve upon, survival is far less easy to ameliorate and probably the sample size has a major influence on this.

The South Western Oncology Group (SWOG) compared cisplatin with cisplatin plus vinorelbine in a large randomised study of 432 patients (415 eligible) [7]. Cisplatin was given at 100 mg/m^2 in both arms and vinorelbine was given at 25 mg/m^2 weekly. Cycles were repeated every 4 weeks. Although haematological toxicity was higher in the cisplatin–vinorelbine arm, response rate, progression-free survival and overall survival were superior in the combination regimen.

Two cisplatin combinations were compared in 228 patients [19]: cisplatin 60 mg/m^2 was given in both regimens. The other drug was epirubicin 120 mg/m^2 for one regimen and vinorelbine 25 mg/m^2 for the other. Both regimens achieved similar response rates and survival, but the high-dose epirubicin resulted in significantly more myelosuppression.

A randomised study from the Italian task force for lung cancer investigated three regimens: cisplatin–vindesine–mitomycin, cisplatin–ifosfamide–vinorelbine and carboplatin–vinorelbine [20]. Although all regimens were well tolerated, the response rate was rather disappointing being lower than 20%.

A large international study has been published, comparing cisplatin alone to a combination of agents; in this study, cisplatin and tirapazamine [12]. Tirapazamine is a novel cytotoxic agent with high selective toxicity against hypoxic cells. There are data indicating that tumour hypoxia may be responsible

for resistance to drugs and radiation. Cisplatin was given at a dose of 75 mg/m^2 in both arms and tirapazamine was administered at 390 mg/m^2 as a 2-hour infusion. Both regimens were given every 3 weeks. This study demonstrated a significant superiority of the combination arm in terms of response rate and survival. The tirapazamine arm was associated with higher frequencies of acute reversible hearing loss, muscle cramping, diarrhoea, skin rash, and nausea and vomiting ($P = 0.001$). However, this apparently did not translate in a worsening of performance status relative to the cisplatin alone arm.

There have been two large studies investigating the role of paclitaxel in combination with cisplatin [13,14]. The first published [13] was an EORTC study comparing cisplatin 80 mg/m^2 in addition to teniposide (VM26) 100 mg/m^2 given on days 1, 3 and 5, to the combination of cisplatin (same dose) with paclitaxel 175 mg/m^2 given as a 3-hour infusion of day 1. Both regimens were repeated every 3 weeks. This study showed a higher response rate in the paclitaxel arm, but no difference in survival or time to progression. In addition the paclitaxel arm fared better than the teniposide arm in terms of severe haematological toxicity, with a significant lower degree of severe leucopenia, neutropenia, thrombocytopenia and anaemia, febrile neutropenia and infection. On the other hand, the paclitaxel arm had more hypersensitivity reactions, myalgia/arthralgia and peripheral neurotoxicity, all significant, but, in general, at very low levels. Furthermore, QoL, assessed using the EORTC questionnaire with the lung cancer module on a total of 104 patients, showed a significant improvement on several functioning scales (emotional, cognitive, social functioning, and global health care), and also fatigue and appetite loss were better in the paclitaxel arm ($P = 0.006$ and <0.001, respectively). However, this difference was shown only at a 6-week assessment, and was later lost. This finding is certainly complicated by the reduced number of patients at risk and completing the questionnaire at later time points. In conclusion, the EORTC lung cancer group elected the cisplatin-paclitaxel arm as the standard arm for their new randomised trial, based on the better response rate, lower severe toxicities, and better quality of life, despite the absence of improved survival. A cost-analysis of this EORTC study reported that costs were similar in the two arms [21], assessed in 4 countries in Europe.

The second randomised trial employing paclitaxel in combination with cisplatin was performed by the ECOG [14]. In this 3-arm study, cisplatin was given at 75 mg/m^2 on day 1, and etoposide was given at 100 mg/m^2 on days 1, 2 and 3, on the first arm of the trial (control arm), cisplatin (same dose) was combined with paclitaxel given at 250 mg/m^2 as a 24-hour infusion on day 2 on the second arm of the trial with granulocyte-colony stimulating factor (G-CSF) support 5 mcg/kg from day 3 to granulocyte recovery; cisplatin (same dose) was combined with paclitaxel 135 mg/m^2 as a 24-hour infusion on day 2 on the third arm of the trial. All regimens were repeated every 3 weeks. This study showed a significant improvement in response rate of both paclitaxel-containing regimens compared to the control arm. However, none of the paclitaxel arms were superior in survival to the control arm when they were used separately in the comparison. Only when the data for the two paclitaxel arms were combined and compared was a significant improvement of survival visible ($P = 0.048$). Similarly, the difference between the control arm and the combined paclitaxel arms was more significant in terms of failure-free survival ($P = 0.007$). Toxicity was significantly worse in the paclitaxel arms, concerning severe granulocytopenia, peripheral neurotoxicity, and myalgias, and this difference was particularly significant in the high-dose paclitaxel arm. QoL was also assessed in this study in 94% of patients, with the use of the FACT-L instrument: although there was a clear decrease in quality of life with time, this was similar in all 3 arms of the study.

A cost-effective analysis was performed of this study by Canadian investigators [22]. They showed that the cisplatin–paclitaxel arm, if paclitaxel was given as a 3-hour infusion, and as an outpatient regimen, may be cost-effective, in the Canadian health system.

A recent ECOG study, presented at the ASCO 2000 meeting, but as yet not published, compared 3 novel regimens with cisplatin–paclitaxel, which had become standard treatment for the group. The three experimental arms were cisplatin–gemcitabine, cisplatin–docetaxel and carboplatin–paclitaxel. There were no significant differences in survival between the novel regimens and cisplatin–paclitaxel. The cisplatin–gemcitabine arm had a significant longer time-to-progression, but the carboplatin–paclitaxel arm was less toxic [23]. This study stresses once more how difficult it is to really make any progress in advanced NSCLC by chemotherapy based on platinum compounds and one of the novel cytotoxics.

In a randomised phase II study, two regimens were investigated by Comella et al. [24]. Patients were randomised between cisplatin 50 mg/m^2, gemcitabine 1 g/m^2 and vinorelbine 25 mg/m^2 given on days 1

and 8 of a three-weekly cycle, or to receive cisplatin 80 mg/m^2, epirubicin 80 mg/m^2 and vindesine 3 mg/m^2 all given on day 1, plus lonidamine 150 mg three times daily. A total of 111 patients were randomised and later 30 additional patients were treated on the first arm. Among the 87 patients treated on the cisplatin–gemcitabine–vinorelbine arm the response rate was 57%, and 37% in the second arm. Progression-free survival and median survival in the two arms were 32 and 50 weeks on the first arm and 18 and 33 weeks in the second arm. Haematological toxicity, however, was also higher in the first arm. This arm was further selected for a phase III study by this group.

A recently reported interim analysis of the phase III study from Italy compared a three drug regimen (cisplatin, gemcitabine, vinorelbine) with cisplatin–gemcitabine and cisplatin–vinorelbine [25]. Cisplatin was given at a dose of 50 mg/m^2 on days 1 and 8, together with 1 g/m^2 of gemcitabine, and 25 mg/m^2 of vinorelbine, in the first arm of the study, repeated every 3 weeks. The second arm contained cisplatin 100 mg/m^2 on day 1 and gemcitabine 1 g/m^2 on days 1, 8 and 15, every 4 weeks. The third arm included cisplatin 120 mg/m^2 on day 1 and vinorelbine 30 mg/m^2 weekly, every 4 weeks. When 60 patients per arm were evaluated for survival an interim analysis was performed, which showed that the third arm was significantly inferior to the three-drug regimen in terms of survival, by multivariate analysis. This arm was therefore discontinued and the trial is still ongoing with the two remaining arms into a full blown phase III trial. The three-drug regimen was not substantially more myelotoxic than the other two arms. The early closure of the third arm based on a relatively small number of patients in a typical phase II randomised setting raises concerns on the untoward use of an interim analysis.

A study in elderly (>70 years) patients has been reported comparing gemcitabine 1200 mg/m^2 and vinorelbine 30 mg/m^2 given on days 1 and 8, versus vinorelbine alone at the same dose. Cycles were repeated every 3 weeks. At an interim analysis on the first 120 patients randomised, a significant difference in survival was observed (with better survival for the combination group) by multivariate analysis and the accrual to the study was terminated. Combination chemotherapy was associated with a delayed deterioration and QoL [26]. Rather worrying in this study was the result obtained by the control arm (vinorelbine alone), which in a previous study was reported to achieve a median survival of 28 weeks [2], in this study it performed as badly as the best supportive care arm of the previous study.

A large phase III study investigated carboplatin–cisplatin with or without ifosfamide [27] in 529 patients with advanced NSCLC. This study showed similar toxicity in both arms, a significantly higher response rate in the three drug-arm, but a similar time to progression and survival.

A randomised phase II study of the Cancer and Leukaemia Group B (CALGB) suggested that non-platinum combinations achieve very similar results to the platinum combinations [28]. Randomised studies of non-platinum combinations are warranted and some are already running.

Phase II trials with 'novel chemotherapy agents'

Numerous phase II studies of various combinations of novel cytotoxic agents have been reported in the past few years. Several reports were dose-finding studies, followed by phase II studies in advanced NSCLC. Although most combinations so far included cisplatin or carboplatin, several new studies seem to indicate substantial activity of non-platinum-based combinations. Of course, only randomised studies will be able to define the benefits of these novel combinations in comparison to those combinations that are platinum-based.

The activity of gemcitabine, paclitaxel and docetaxel as single-agents has been confirmed by at least 2 studies per agent; the activity of vinorelbine, however, appeared to be rather disappointing in a study in which only patients older than 70 years were included [29]. Another study in elderly patients showed a 22% response rate with gemcitabine [30]. These studies highlight the importance of conducting specific trials in elderly patients, as they probably require less aggressive treatment than young good-performance status patients. Treatments with single agents, which are well tolerated, appear to be adequate for this patient population.

Most patients who are fit to receive chemotherapy usually receive combinations of at least two agents. Among the platinum-combinations, cisplatin combined with gemcitabine, paclitaxel, docetaxel or vinorelbine and the combination carboplatin–paclitaxel have been investigated in at least two studies, and significant activity has been confirmed. Of interest is the combination of carboplatin with gemcitabine. In fact, a study from the US was terminated because of excessive thrombocytopenia [31]. In another study from Italy [32], a proper phase I study was performed which identified feasible doses for phase II studies and a small phase II study was also reported with this combination, with promising results. A major difference between the two studies is the different regimen

utilised, in fact the Italian study used 2 administrations of gemcitabine only vs 3 in the American study; moreover, carboplatin, although given at the same dose, was administered on day 8 instead of on day 1 in the Italian study. These apparently minor differences may have a profound influence on the development of thrombocytopenia.

Among the non-platinum doublets, several are now available, with different toxicity profiles. The combination paclitaxel–gemcitabine has received lots of attention, because of its relatively good tolerability and as it can be given in an outpatient setting. In a phase I–II study [33], pharmacokinetics was also evaluated. No drug-drug interactions were observed, but both drug concentrations were related to pretreatment hepatic function, and the gemcitabine Cmax was related to the amount of thrombocytopenia observed with this combination [34].

Five studies of the combination of gemcitabine and vinorelbine have been reported in the past 2 years, showing remarkable activity and good tolerability [35–39].

Combinations of three or more anticancer agents are also being tested. Most of these combinations contain either cisplatin or carboplatin. Amongst the best investigated triplets are those with paclitaxel and gemcitabine in combination with cisplatin or carboplatin. The response rates are, in general, higher than those reported by doublets, with reasonable toxicity and dose intensity. Also, survival appears to be promising in several of these phase II studies. Results of randomised studies will clarify whether these apparent advantages are real.

Second-line chemotherapy

As first-line chemotherapy is now standard treatment for advanced NSCLC patients, the use of second-line chemotherapy has also been investigated intensively in recent years. In general, response rates are lower than in first-line, and single agents are probably better tolerated than combinations. Several relatively small phase II studies indicate some activity for many of the more novel cytotoxic agents. A large study of 83 previously treated patients with advanced NSCLC received gemcitabine weekly for 3 weeks, followed by a week's rest [40]. Of these patients, 34 had locally advanced stage III disease. The treatment was well tolerated, and partial responses were obtained in 19% of patients. This suggests similar activity of this agent in first- and second-line therapy.

A large phase II study of docetaxel has been reported in patients previously treated with platinum-based chemotherapy [41]. Docetaxel was given at 100 mg/m^2 and of 80 patients enrolled in the study 47 (59%) were refractory to platinum therapy. A response rate of 16% was obtained, and response was similar in patients who were sensitive or refractory to platinum. Median survival was 7 months and 1-year survival was 25%. Grade IV neutropenia was observed in 77% of patients, but no toxic deaths occurred in this multicentre study.

Two large randomised studies have demonstrated that docetaxel is better than standard second-line chemotherapy in advanced NSCLC [42] or best supportive care [43]. Table 2 summarises the results obtained with docetaxel in these randomised studies, which resulted in docetaxel being registered for second-line therapy in advanced NSCLC. Study TAX 320 [42] compared docetaxel at 100 mg/m^2 (D100) or 75 mg/m^2 (D75) or to a choice of 'standard chemotherapy' consisting of vinorelbine 30 mg/m^2 weekly or ifosfamide 2 g/m^2/day on days 1 through 3. All cycles were of 3 weeks. A total of 373 patients were enrolled, 125 into each of the docetaxel arms and 123 into the control arm (89 vinorelbine and 34 ifosfamide). Patients had to have failed on one or more platinum-containing chemotherapies. Prior treatment with paclitaxel did not exclude the patient from study. Patients in the docetaxel 75 mg/m^2

Table 2
Second-line randomised studies of docetaxel in advanced NSCLC

Drug/dose	D100	D75	V/I	D100	D75	D100 + 75	BSC
Patients	125	125	123	49	55	104	100
Response%	10.8	6.7	0.8	6.3	5.5	5.8	–
MRD months	7.5	9.1	5.9	5.6	6.1	6.1	–
TTP (months)	8.4	8.5	7.9			10.6	6.7
MST (months)	5.5	5.7	5.6	5.9	7.5	7.0	4.6
1-year survival (%)	21	32	19	19	37	29	19
Febrile neutropenia (%)	12	8	1	22.4	1.8	11.5	–
Reference	Fossella [42]			Shepherd [43]			

D = docetaxel (mg/m^2); MRD = median response duration; TTP = time to progression;MST = median survival time; NR = not reported, NSCLC, non-small cell lung cancer;BSC, best supportive care, V/I, vinorelbine/ifosfamide.

arm remained in the study the longest, including those who received a higher dose of docetaxel. Response rates were very low in all arms. However, they were significantly higher in both docetaxel arms than in the control arm ($P = 0.001$ and $P = 0.036$ for D100 and D75 vs the control group, respectively; $P = 0.002$ for combined D arms vs control). Overall time to progression favoured treatment with docetaxel, which reached significance for D100 vs control ($P = 0.044$) and for both docetaxel arms vs control ($P = 0.046$), but not for the D75 arm vs control arm ($P = 0.093$). Although the median survival times were similar in the three arms, survival curves actually separated after approximately 8 months of observation and the 1-year survival was significantly longer for the D75 arm vs control ($P = 0.025$), but D100 had a similar 1-year survival to the control arm. There was a trend for better response and survival in patients with platinum-resistant tumour compared to platinum-refractory, whereas prior exposure to paclitaxel (35%) did not influence response or survival. Grade 4 neutropenia was more frequent in the D100 arm (77% of patients) than in the D75 arm (54%) or the control arm (31%); this led to a significantly higher use of filgastrim in the D100 arm (28% of cycles in D100, 7% in D75 and 3% in control). The incidence of treatment-related death was low and similar between the 3 arms (2%, 2% and 0%, respectively). There was a trend for patients in the high dose docetaxel group to discontinue treatment more frequently because of toxicity, although this did not reach statistical significance (12.8%, 7.2% and 4.1%, respectively). Although assessment of quality of life was performed in this study, this was not yet available at the time of publication of this report, although the authors stated that this was improved with docetaxel treatment.

A second randomised study (TAX 317) allotted patients with advanced NSCLC previously treated with platinum-based chemotherapy to receive 100 mg/m^2 docetaxel or best supportive care (BSC) [43]. Patients were not allowed to have received prior taxanes, but could have received more than one prior regimen of chemotherapy. Interim safety-data monitoring identified a high toxic death rate on chemotherapy, and this led to a protocol amendment to a reduced dose of docetaxel to 75 mg/m^2. In total 204 patients were randomised, 100 to BSC and 104 to docetaxel; 49 received D100, and 55 received D75. The response rate to docetaxel was also low in this study with only a 5.8% partial response rate in the total patient population treated with both doses by intent to treat analysis (7.1% when considering only the patients with measurable lesions). Time to progression was significantly longer for the docetaxel-treated patients ($P = 0.001$) and this effect was observed for both docetaxel dose levels (D100, $P = 0.037$; D75, $P = 0.004$). Survival of patients treated with docetaxel was significantly longer than those in the BSC arm ($P = 0.047$); however, this difference was only significant for the D75 dose, compared with BSC ($P = 0.01$). In this study, there was a striking difference in toxicity between the 2 doses of docetaxel; in particular D100 induced a much higher incidence of febrile neutropenia, and 5 out of 6 patients who died within 30 days of receiving chemotherapy for causes unrelated to treatment were in the D100 arm. Also, in this study, quality of life was assessed, but was not presented as part of this paper. In any case, significant improvements of pain and fatigue were reported with the administration of docetaxel. This led to a reduced requirement for medications. Both studies were important for the FDA registration of docetaxel for the second-line treatment of NSCLC.

Novel treatment modalities

A recent review described the development of novel molecules targeted to specific molecular alterations present in lung cancer [44]. These agents target growth factors and growth factor receptors (e.g. antibody against the Her2/neu oncogene, such as herceptin, antibody against the epidermal growth factor receptor (EGFR), such as C225 and many others).

Several small feasibility studies of gene transfer also indicated that this approach may have some activity in the treatment of locally advanced tumours [45], but major limitations do still exist in treating patients with advanced metastatic disease. One of these studies applied adenoviral-mediated *TP53* gene transfer in combination with cisplatin chemotherapy [46].

Small cell lung cancer

Relatively little progress has been made in small cell lung cancer in the past two decades. The most important advances in the treatment of SCLC are radiotherapy to the chest and prophylactic cranial irradiation (PCI) in patients with limited disease. These will be described in another chapter. This chapter will mainly deal with chemotherapy treatment of SCLC, and, more pertinently, for patients with extensive disease, where a combined modality is rarely indicated. Despite years of clinical research, the prognosis for extensive disease small cell lung cancer has been improved only minimally: data from the Surveillance, Epidemiology and End Results (SEER) database

Table 3
Chemotherapy regimens for SCLC

- PE (cisplatin/etoposide)
- PEV (cisplatin/etoposide/vincristine)
- CE (carboplatin/etoposide)
- ICE (ifosfamide/carboplatin/etoposide)
- PE followed by CAVE
- CAV (cyclophosphamide/doxorubicin/vincristine)
- CAE (cyclophosphamide/doxorubicin/etoposide)
- CAVE (cyclophosphamide/doxorubicin/vincristine/etoposide)

show that an improvement in median survival from 7 months to 8.9 months ($P = 0.01$) has been obtained from 1972–1994 [47].

The most widely employed combinations of drugs are depicted in Table 3. However, several modifications of doses and slight changes in drug compositions have been made to these original regimens. Unfortunately, not all of these have been properly tested in randomised clinical trials. In general, these regimens are given every 3 weeks, but some combinations require a longer marrow recovery. Platinum (cisplatin)-based regimens are preferred in limited disease, because combinations with radiotherapy are less toxic and the radio-enhancing effect of cisplatin can probably be exploited. However, in extensive disease, several drug combinations are in use, and some do not contain platinum drugs.

The CAV regimen has long been the standard therapy for extensive disease, and there have been two randomised studies testing whether cisplatin–etoposide or the alternation of these two regimens was superior to CAV. One of them [48] randomised 477 extensive disease SCLC patients to receive cisplatin–etoposide, CAV, or the alternation of the 2 regimens. Although the response rate was slightly lower in the CAV arm (51%) than in the cisplatin–etoposide arm (61%), this was not statistically significant, and the complete response rate was similar in the 3 arms (7%, 10% and 7%, respectively) and the survival was also not statistically different (median survival of 8.3, 8.6 and 8.1 months, respectively). A smaller Japanese study on 288 eligible patients, including also limited disease patients, investigated exactly the same question [49]. The response rates for cisplatin–etoposide (78%) and the alternating regimen (76%) were significantly higher than the rate for CAV (55%), while the complete response rates were similar (14%, 16%, and 15%, respectively). The survival time with the alternating regimen (11.8 months) was superior to that with CAV (9.9 months) ($P = 0.027$) or that with PE (9.9 months) ($P = 0.056$). In patients with limited disease, the survival in the alternating arm was significantly superior to the survival in the CAV arm ($P = 0.014$) or the survival in the PE arm ($P = 0.023$). The toxic effects were acceptable in all three chemotherapy regimens. These results favour the alternating chemotherapy over either standard chemotherapy, such as CAV and PE, although the differences were not dramatic.

In general, studies investigating alternating chemotherapy regimens indicate little advantage from this treatment, and alternating chemotherapy has been abandoned by most.

The number of agents in a combination chemotherapy regimen is also a question, which has been asked in several randomised studies. One study demonstrated a significantly superior survival with the addition of ifosfamide to the cisplatin–etoposide regimen in 171 patients with extensive disease SCLC [50]. Although the response rate was similar, both the median survival (7.3 vs 9.1 months) and the 3-year survival (0 vs 5%) were improved ($P = 0.045$) in the three-arm study. However, the ifosfamide-containing treatment was much more myelotoxic than the two-drug regimen and therefore its implementation in routine clinical practice has not really occurred.

Recently, a French randomised study reported the results of a study in which patients were randomly assigned to receive either EP, cisplatin-etoposide ($n = 109$) or PCDE ($n = 117$), etoposide, cisplatin, plus cyclophosphamide and 4′-epidoxorubicin [51]. Patients in the PCDE arm had a statistically significant higher frequency of combined complete plus partial responses compared with those in the EP arm (21% plus 55% versus 13% plus 48%, respectively; $P = 0.02$ for the difference in the combined objective responses). Patients in the PCDE arm survived longer than those in the EP arm (1-year survival rate: 40% and 29%, respectively; median survival: 10.5 and 9.3 months, respectively; $P = 0.0067$). Haematological toxicity was, however, significantly higher in the PCDE arm (22% with documented infections compared with 8% in the EP arm; $P = 0.0038$), and the toxicity-related death rate was 9% in the PCDE arm versus 5.5% in the EP arm ($P = 0.22$). Actually, in both arms of this study the toxic death rate is unacceptably high, and probably the schedule of drugs needs some adjustment in both arms. It is unlikely that the PCDE will become an internationally recognised standard based on these results.

Dose intensification

Dose intensification remains an area of interest in the treatment of SCLC, given the high responsiveness

observed with a broad spectrum of anti-neoplastic agents with varying mechanisms of action. Administering drugs with overlapping toxicities sequentially with appropriate supportive measures, such as haematopoietic growth factors and prophylactic antibiotics, increases dose intensity and/or dose density. In the past couple of years, significant interest has again been devoted to intensified regimens, after a relatively long period with only a few studies. One of the best tested regimens is the CODE regimen developed by Murray et al. [52]. The favourable results of the initial phase II study led to a phase III study [53] in which CODE was compared to the Canadian standard CAV/PE. A total of 219 good performance status (only 10% Eastern Co-operative Oncology Group (ECOG) performance status 2) extensive disease SCLC patients were enrolled. Near complete responders were offered thoracic irradiation and prophylactic irradiation. Unfortunately, the CODE regimen proved no more effective than CAV/PE in terms of progression-free survival (0.66 years) and overall survival (0.98 years). Ten percent of patients were progression-free at two years. Toxicity was quite different between the two arms: 8.2% treatment-related fatality rate in the CODE arm versus an acceptable 0.9% in the standard arm. This trial was closed prematurely due to this difference in toxicity. A nearly identical Japanese study [54] produced similar results: no difference in response rate (76.1% vs 85.1%) median survival (11.6 months vs 10.9 months) and long-term survival, for the CODE and the CAV/PE arms respectively. Despite the routine administration of G-CSF, haematological toxicity was significantly increased in the CODE arm with a 3.5% fatality rate due to neutropenic fever compared to 0% in the CAV/PE arm.

At odds with these results is the study reported by Steward and coworkers [55], in which 300 good- or intermediate-prognosis SCLC patients were randomised to receive six cycles of ifosfamide 5 g/m^2, carboplatin 300 mg/m^2, etoposide 120 mg/m^2 intravenously (i.v.) days 1 and 2 and 240 mg/m^2 orally day 3, and vincristine 0.5 mg/m^2 i.v. day 15 (V-ICE) every 3 weeks or every 4 weeks, followed by a second randomisation to granulocyte macrophage-colony stimulating factor (GM-CSF) support or placebo. The decision to give thoracic radiotherapy and PCI for patients in complete response was left to the discretion of the individual centres. Although the study was designed to test the hypothesis that GM-CSF support would reduce the incidence of complications from myelosuppressive chemotherapy, which actually did not occur, interestingly an increase in both median (443 day vs 351 days, $P = 0.0014$) and 2-year survival (33% vs 18%) was observed in the intensified arm. PCI and chest radiation significantly contributed to the therapeutic outcome.

The Molecular Research Council (MRC) recently reported the results of a large randomised study in which patients were randomised to receive doxorubicin, cyclophosphamide, and etoposide every 3 weeks or every 2 weeks with G-CSF support [56]. The dose intensity in the intensified arm was 34% higher and response rates were significantly higher as well (40% vs 28%, $P = 0.02$). Survival was also significantly longer in the intensified arm ($P = 0.04$) with a one-year survival of 47% vs 39%. Interestingly, palliation and QoL were similar in the two arms. This important study confirms that small benefits may be achieved by a relatively small dose intensity increase.

Further dose escalation of the ICE regimen was investigated by Leyvraz et al. [57]. Here, a group of 69 good performance SCLC patients, of whom 30 had limited disease, were treated with three courses of ifosfamide 10 g/m^2, carboplatin 1200 mg/m^2, etoposide 1200 mg/m^2 i.v. divided over 4 days every 4 weeks. Peripheral blood progenitor cells were harvested before treatment and mobilised with epirubicin 150 mg/m^2 and filgastrim. Again, radiotherapy policies among the participating centres were not uniform. The planned dose escalation over standard ICE was 310%, but only 94% was accomplished. The regimen could be delivered at the expense of a 9% treatment-related fatality rate, which the authors felt was within an acceptable range before embarking on phase III testing. Median survival was 13.5 months with 32–42% of limited disease patients and 5% of extensive disease patients alive at 2 years. Of note is the high incidence of brain relapses as the first site of recurrence (30%) suggesting a role for routine PCI. At first glance, these results are comparable to the intensified arm in the Steward study in which a modest 26% dose escalation over conventional V-ICE was delivered. Whether early dose intensification in the range studied by Leyvraz et al. is of therapeutic relevance needs to be addressed in randomised comparisons. Such a study is presently running in European centres.

New agents/novel regimens

In the past 2 years several new agents have been investigated in patients with SCLC; most testing is being done in previously treated patients, but a few studies still employ selected untreated patients with extensive disease or unfit patients, who were not previously treated by chemotherapy.

The novel oral platinum analogue JM 216 given at 120 mg/m^2 days 1–5 every 3 weeks, was tested in a phase II study including 27 chemonaive SCLC patients, 10 with limited disease unfit to receive combination chemotherapy and 17 with extensive disease [58]. Ten partial responses (37%, 95% confidence interval (CI) 19–58%), but no complete responses were observed, and the median survival time was 210 days. Toxicities were uncommon.

Another platinum analogue, SKI 2053R, was administered to 38 patients with untreated extensive disease SCLC [59]. After treatment with 400–440 mg/m^2 SKI 2053R every 3–4 weeks, 6 of 37 patients, that could be evaluated, achieved a partial response (16.2%, 95%CI 4.4–28.0%). Estimated median survival was 7.4 months. Side-effects, especially nephrotoxicity, were uncommon. Although both platinum analogues have some activity, it is unlikely that they will make a major contribution to the treatment of SCLC.

Both currently available taxanes were tested in phase II studies. A phase II study by SWOG [60] evaluated the efficacy of docetaxel 100 mg/m^2 every (q) 3 weeks in 47 (43 eligible) untreated extensive disease SCLC patients. Ten partial responses (23%, 95% CI 12–39%) and a median survival of 9 months were observed. Kirschling et al. [61] enrolled 43 untreated extensive disease SCLC patients in a phase II study of paclitaxel given at 250 mg/m^2 by 24-hour infusion plus G-CSF support; a 53% response rate was reported with a median survival time of 9 months.

Following the establishment of single agent activity of paclitaxel in SCLC, phase I studies were reported with the addition of paclitaxel to EP. Kelly et al. [62] found the maximum tolerated dose (MTD) of this combination to be paclitaxel 175 mg/m^2 (3-hour infusion), cisplatin 80 mg/m^2, etoposide 80 mg/m^2 all given i.v. on day 1, followed by etoposide 160 mg/m^2 orally (p.o.) days 2–3 with G-CSF support. The dose-limiting toxicity of this regimen was peripheral neurotoxicity. A 83% response rate with 22% complete responses were observed in a cohort of 28 extensive disease SCLC, of whom 23 were evaluated for response. Similar results were obtained in a phase I/II study conducted at MD Anderson [63]. In this study, the MTD was reached at paclitaxel 135 mg/m^2, cisplatin 75 mg/m^2 and etoposide 80 mg/m^2 days 1–3. Here, myelosuppression was dose-limiting, probably due to the fact that CSF's were not routinely administered. The overall response rate in the phase II part of this study was 90% of 38 assessable patients with a median survival of 47 weeks.

A Canadian study [64] identified the MTD of gemcitabine added to EP to be cisplatin 75 mg/m^2 and etoposide 50 mg/m^2 days 1–5 and gemcitabine 800 mg/m^2 days 1 and 8 every 3 weeks. In a group of 20 SCLC patients, both treated and untreated, the response rate was 54%, and the untreated patients had a 75% response rate. Glisson et al. [65] reported the results of a phase II study with a modified PIE schedule. Cisplatin was given at 20 mg/m^2, ifosfamide 1500 mg/m^2 (days 1–3), and oral etoposide 50 mg/m^2 (days 4–17) every 4 weeks. Among 30 evaluated extensive disease SCLC patients, 5 (17%) complete responses and 23 (77%) partial responses were observed and the overall survival duration was slightly in excess of 1 year.

A new regimen of interest is the combination of irinotecan and cisplatin: Japanese researchers [66] administered cisplatin 60 mg/m^2 on day 1 and irinotecan 60 mg/m^2 on days 1, 8, 15 to 75 SCLC patients including 40 limited disease patients who received chest radiotherapy after course 4. The response rate was 84% with 29 complete responses. Median survival for limited disease patients was 14.3 months and 13.0 months for those with extensive disease 13.0 months. Five limited disease patients who received radiotherapy to the chest, in addition to the chemotherapy, developed severe radiation pneumonitis and 2 of these died. The results in extensive disease patients were, however, very promising, as this represents a more than 3 months increase in the median survival of these patients, compared with standard chemotherapy. Recently, at ASCO 2000, a randomised study in patients with extensive disease SCLC was presented, which compared cisplatin–etoposide to cisplatin–irinotecan [67]. This study confirmed an improved survival by the novel combination chemotherapy: the 2-year survivals were 18.9 vs 6.5% for the irinotecan–cisplatin and the etoposide–cisplatin arms, respectively ($P = 0.0021$). In total, 154 patients were enrolled in the study and the study was closed after an interim analysis showed superior results in the irinotecan–cisplatin arm. Two confirmatory randomised studies are presently under way.

Gridelli et al. [68] treated 43 extensive disease SCLC patients with a combination of carboplatin 300 mg/m^2 and vinorelbine 25 mg/m^2 days 1 and 8 every 4 weeks, for a maximum of 6 cycles. Thirty-two responses (10 complete, 22 partial), for a response rate of 74% (95% CI 59–86%) were observed and the median survival rate was approximately 9 months. Grade 4 toxicities were not encountered in this phase II trial and the authors concluded that this novel regimen might be a reasonable alternative for more toxic cisplatin-based regimens.

The ECOG tested the efficacy of all-*trans*-retinoic acid added to standard PE chemotherapy [69]. The trial was based on the preclinical finding that ATRA inhibits growth and *myc/ras*-mediated phenotypic transition to treatment resistance in a laboratory SCLC model. Twenty-two untreated extensive disease SCLC patients were to be treated with ATRA 150 mg/m^2/day for 1 year in addition to standard PE. The median duration of ATRA treatment, however, was only 2.8 months as 13/22 patients discontinued treatment due to mucocutaneous changes and headaches. The response rate was also disappointing (45%, 95 CI 24–68%) and the median survival was 10.9 months.

Wood et al. [70] conducted a phase III trial aimed at reversing P-glycoprotein-mediated drug resistance by the addition of megoestrol acetate to alternating CAV/PE. A total of 130 SCLC patients were randomised, but no difference in survival was observed.

Immunotherapy may hold some promise in this disease. Grant et al. [71] evaluated immunisation using the anti-idiotypic antibody BEC2, which mimics the ganglioside GD3 expressed on the surface of most SCLC. Fifteen SCLC patients received, after completion of standard therapy, 5 intradermal immunisations with BEC2 combined with Bacillus Calmette Guerin (BCG). For 8 limited disease patients and 7 extensive disease patients median survival times were >47 months and 11 months, respectively, which the authors felt to be a substantial improvement in comparison to their previous experience in a similar group of patients. A large randomised study has been launched recently by the EORTC, in which patients with limited disease in response after chemotherapy and radiation are randomised to be followed-up, or to receive vaccination with BEC2/BCG, as performed in this small trial.

Elderly and infirm SCLC patients

Elderly and poor performance status SCLC patients are, in general, under-represented in clinical trials. There is, in general, little emphasis on this issue in clinical trials, whereas in NSCLC this problem has been addressed already. A few phase II studies have been recently reported, in which toxicity has been kept under control as much as possible. Two studies sought to minimise myelotoxicity of the carboplatin–etoposide regimen by using a pharmacodynamic based formula of carboplatin dosing in this patient group. Matsui et al. [72] treated 38 elderly (median age 78 years, range 73–84 years) with oral etoposide 40 mg/m^2 days 1–14 and carboplatin dosed (Egorin's formula minus 20%) at a desired platelet nadir count of 75 × 10^9/l, every 4 weeks for 4 cycles. The majority of patients could receive the planned carboplatin dose, and there were 14% grade 4 thrombocytopenias and 2 treatment-related deaths. The objective response rate was 81%, with median survival times of 15.1 months for limited disease patients and 8.6 months for extensive disease patients. A similar approach was used by Okamoto et al. [73] who treated 36 elderly patients (median age 73 years, range 70–80 years). Here, the Calvert's formula was used to dose carboplatin (area under the concentration curve AUC 5) combined with etoposide 100 mg/m^2 days 1–3 every 4 weeks for 4 courses. Myelosuppression was the principle toxicity, but only 1 patient experienced febrile neutropenia and no haemorrhagic complications were observed. Dose reductions were performed in 8% of patients, mainly due to grade 4 neutropenia. The objective response rate was 75% (95 CI 61–89%) with median survival times of 11.6 months for limited disease and 10.1 months for extensive disease patients. In both studies, limited disease patients received chest radiation after completion of chemotherapy.

SWOG [74] conducted a phase II study with an all oral regimen consisting of oral cyclophosphamide (50 mg td) and oral etoposide (50 mg td) days 1–14 every 4 weeks. Treatment was administered to 39 poor performance status patients with extensive disease SCLC. A 41% response rate was obtained with median survival time of 7 months.

Canadian researchers [75] developed the PAVE regimen for elderly SCLC patients; its rationale including decreased toxicity and logistic considerations (eg. less hospital visits). Sixty-six elderly (all >65 years) SCLC patients were treated with cisplatin 30 mg/m^2, doxorubicin 40 mg/m^2, vincristine 1.0 mg/m^2, etoposide 100 mg/m^2, all given on day 1, and oral etoposide 100 mg/m^2 given on days 3–5 every 3 weeks for 4 cycles. Limited disease and selected extensive disease patients received chest radiation during the second cycle concurrently with PE; PCI was administered to complete responders. Approximately two-thirds of patients received the planned treatment programme without dose reductions. The incidence of haematological complications was low and only one treatment-related death was observed. Response rates (limited disease 92%, extensive disease 87%) and median survival times were comparable to those published for standard regimens. For limited disease patients, median survival was 70 weeks and the 5 year survival rate was 25%, whereas median survival for extensive disease patients was 46 weeks.

The same group [76] presented their experience with an abbreviated CAV/PE regimen (2 cycles)

and chest radiotherapy delivered to elderly or poor performance status limited disease SCLC patients. A surprising 51% complete response rate (clinically staged) was obtained with 28% and 18% of patients alive at two and five years, respectively. The authors concluded that the benefit of treatment is conferred by the first two treatment cycles without compromising long-term survival. However, they felt that fit elderly limited disease SCLC patients should receive standard management.

In general, there is need for well designed studies that particularly address the issue of adequate treatment for elderly and infirm SCLC patients.

Treatment at relapse

At relapse SCLC patients may be distinguished into sensitive patients (>3 months off induction treatment) and refractory (progressing <3 months off induction treatment) [77]. This is a relatively recent distinction, which allows testing of novel agents in previously pretreated patients with sensitive disease, with an expectancy of response which is not much lower than that of untreated patients. This consideration enables the important ethical aspects of treating SCLC patients with novel agents to be avoided at the start of the treatment.

The sensitive patient group was recently the subject of the only randomised trial in relapsed SCLC published to date. Von Pawel et al. [78] randomised 221 patients to receive CAV or topotecan (1.5 mg/m^2 days 1–5 q 3 weeks) and observed a 24.3% response rate with single agent topotecan versus 18.3% with CAV ($P = 0.522$) with similar median survival times (25 vs 24.7 weeks, $P = 0.795$). The incidence of grade 4 neutropenia significantly favoured treatment with topotecan, as did symptom improvement. This study and a number of non-randomised phase II studies of topotecan resulted in this drug being registered in several countries in the world for patients with sensitive relapse SCLC.

Non-randomised trials showed a remarkably high activity in a Japanese study [79] evaluating etoposide 80 mg/m^2 given on days 1–3 and irinotecan 70 mg/m^2 given on days 1, 8, 15 with G-CSF support. A response rate of 71% (95% CI 53–89%) and median survival of 271 days were observed among 25 relapsed SCLC patients.

In refractory relapses after CDE chemotherapy, the combination of carboplatin administered at a targeted AUC 7 and paclitaxel 175 mg/m^2 produced a 73.5% response rate (95% CI 59–88%), with a median survival of 31 weeks [80]. The value of this regimen after failure of the more commonly used PE regimen needs further investigation. In a similar group of patients, single agent gemcitabine (1000 mg/m^2 days 1, 8, 15) produced a meagre 13% response rate (95% CI 6–27%) with a median survival of 17 weeks [81].

Paclitaxel was combined with doxorubicin in a study of 46 recurrent SCLC patients [82]. Treatment required hospitalisation in 20% of patients due to neutropenic fever. The response rate was 41%, but only 2/14 with refractory disease responded, compared to 52% of the sensitive patients. This study confirms substantial cross-resistance between current antineoplastic agents, including the new generation of agents.

In conclusion, properly designed studies with well characterised patients' features are needed in this area of research.

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