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The role of chemotherapy in the treatment of unresectable stage III and IV nonsmall cell lung cancer

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Lung cancer is the leading cause of cancer-related mortality in the United States [1]. Most patients with lung cancer have nonsmall cell lung cancer (NSCLC) and present with stage III (locally advanced) or stage IV (metastatic) disease. In stage III NSCLC, cure is possible and depends on effective loco-regional control as well as the eradication of occult micrometastatic disease that is present in most of these patients. The latter issue is largely responsible for the ineffectiveness of local modalities alone (surgery and thoracic radiation therapy [TRT]) in curing patients with stage III NSCLC. Incorporation of systemic chemotherapy with either surgery or TRT has lead to improved survival outcomes in patients with stage III NSCLC [2]. The mechanism that is responsible for improved survival in this setting may be either eradication of occult systemic micrometastases [3], or, in the case of TRT, improvements in loco-regional control [4,5]. In stage IV NSCLC, cure is not possible and the goals of therapy include prolongation of survival and palliation of disease-related symptoms [2]. Systemic chemotherapy has been shown to unequivocally accomplish both of these goals in patients with stage IV NSCLC with a good performance status (PS).

This article provides an analysis of the role of systemic chemotherapy in patients with unresectable stage III and IV NSCLC. All patients who are diagnosed with NSCLC should be accurately staged to define the extent of intrathoracic, as well as extrathoracic, disease. Accurate staging is a critical aspect of the management of these patients and should include pathologic documentation of the presence and extent of nodal disease (in the case of stage III NSCLC) and clear documentation of metastatic disease unless the

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clinical information is compelling. The role of systemic chemotherapy will be evaluated in patients with stage IIIB (malignant pleural effusion) and stage IV NSCLC, and in combination with TRT in patients with unresectable stage IIIA/B NSCLC.

Chemotherapy in patients with unresectable stage IIIA/B NSCLC

TRT alone delivered at conventional doses (60–66 Gy) and conventional fractionation schedules (1.8–2.5 Gy/d) results in median survival times of 8 to 12 months and 5-year survival rates of 2% to 9% [5–16]. At best, TRT addresses only the loco-regional aspect of the disease and ignores occult micrometastatic disease that is present in most patients. In studies that use TRT alone, distant recurrences are eventually identified in most patients. When examining how effective TRT alone is in controlling loco-regional disease, the results are rather sobering; loco-regional recurrence is involved in approximately 75% of recurrences. In a landmark trial reported by Arriagada and colleagues [3], loco-regional control was defined radiographically and bronchoscopically. Patients in that trial received 65 Gy of TRT with local control rates of less than 15%. Given this, conventional doses of TRT alone do not effectively address loco-regional control and do not result in meaningful long-term survival outcomes. Strategies that may yield improved outcomes include altered fractionation or accelerated treatment schedules, dose-escalation of TRT, improved tumor targeting using three-dimensional treatment planning, improved tumor localization modalities, and the addition of "radio-enhancing" chemotherapy.

Chemotherapy can be combined with TRT either sequentially or concurrently or both with advantages and disadvantages to all approaches. Theoretically, the sequential approach should avoid overlapping toxicities but prolongs the overall treatment time and delays the initiation of TRT. Preclinical models have raised several concerns about this approach including stimulation of tumor cell repopulation during chemotherapy, increasing the probability of cross-resistant tumor cells, and stimulation of distant metastases [17]. These concerns would be less serious with the concurrent administration of chemotherapy. The optional dosing strategy of chemotherapy delivered concurrently with TRT is not known, however, and concurrent approaches have included continuous, daily, weekly, biweekly or every 3 to 4 week chemotherapy administration schedules. Other advantages of the concurrent approach include reduced treatment times and the use of chemotherapeutic agents as "radiation-enhancers".

Before examining trials of chemotherapy and TRT in patients with unresectable stage IIIA/B NSCLC, a brief discussion about patient selection seems appropriate. Despite the revised staging system [18], stage IIIA/B NSCLC remains a heterogenous disease. There has been some debate about the prognostic implication of IIIA versus IIIB in patients who were treated with TRT alone; most trials showed improved survival outcomes for

patients with IIIA [19,20]. In addition, the degree of intrathoracic staging (particularly mediastinoscopy) as well as extrathoracic staging was not standard among the trials. In general, patients who were included in these trials had a good PS (Eastern Cooperative Oncology Group [ECOG 0–1]) and had minimal weight loss. These points are pertinent as one evaluates patients for combined modality therapy as it carries the risk of increased toxicity. Table 1 shows the major phase III trials reported to date in which TRT alone was compared with either sequential or concurrent cisplatin-based chemotherapy and TRT. One of the most important trials was the "Dillman" trial that was performed by the Cancer and Acute Leukemia Group B (CALGB) [9]. This trial was of a simple design and randomized ECOG PS 0–1 patients with less than 5% weight loss to either TRT alone (60 Gy) or sequential cisplatin/vinblastine for two cycles followed by the same doses of TRT. The median survival was increased from 9.6 months to 13.7 months ($P = 0.012$) and the 5-year survival was increased from 6% to 17% for TRT alone arm and the chemotherapy/TRT arm, respectively (Fig. 1). Subsequently, the Radiation Therapy Oncology Group (RTOG) [14], as well as trials in Europe also of a sequential design [11], confirmed the findings of the CALGB trial. The analysis of several of these trials [3,14,21] suggested that a reduction in the occurrence of systemic metastases was the mechanism responsible for improved survival. Also, two trials [4,5] that used concurrent chemoradiotherapy versus TRT alone improved median and long-term survival. Both of these trials used either daily or weekly chemotherapy administration schedules; the investigators suggested that the improvement in survival was the result of enhanced control of loco-regional disease. Whether pursuing sequential and concurrent chemo-radiotherapy in this setting yields better outcomes has not been explored. This is the focus of the current CALGB trial (CALGB 39801) in which patients are randomized to either concurrent chemoradiotherapy alone or sequential and concurrent chemoradiotherapy (Table 2).

As noted earlier (see Table 1), not all randomized trials have yielded positive results [6,7,13,15]. This may be the result of poor trial design as some trials included poor PS patients or earlier stage patients, or less effective chemotherapy regimens. It is also likely that, although real, the absolute benefit from the addition of chemotherapy to TRT is small and may not be statistically significant in every trial. To address this issue, three meta-analyses [22–24] were performed that used the data from published randomized trials [22,24] and individual patient data from published as well as unpublished trials [23]. All three meta-analyses reported a statistically significant survival benefit with cisplatin-based regimens in chemoradio-therapy strategies. The relative risk of death at 2 years was reduced between 13% and 30% in these three meta-analyses. The issue of optimal schedule (sequential vs concurrent) was addressed in only one of the meta-analyses [24] with no apparent difference in the magnitude of the benefit when comparing sequential versus concurrent approaches.

Table 1
Phase III trial of TRT and TRT plus sequential or concurrent platinum-based chemotherapy

				Survival						
				(mo)		2-yr (%)		5-yr (%)		
Author [ref]	n	Chemotherapy	TRT (Gy)	TRT	CH/TRT	TRT	CH/TRT	TRT	CH/TRT	*P*
Sequential										
Dillman et al [9]	155	VbP	60	10	14	13	26	6	17	0.01
Miller et al [13]	229	FVMCAP	58	9	9	18	13	3	4	NS
Mattson et al [12]	238	CAP	55	10	11	17	19	–	–	NS[a]
Sause et al [14]	303	VbP	69.6 HF	12	14	24	32	6	8	0.04
Sause et al [14]	300	VbP	63	11	14	19	32	5	8	0.04
Brodin et al [7]	330	EP	56	9	9	–	–	–	–	NS[b]
LeChevalier et al [11]	353	VdCPU	65	10	12	14	21	4	12	0.02
Cullen et al [8]	446	MIC	50[c]	10	12	16	20	8[d]	12[d]	0.14
Concurrent										
Schaake-Koning et al [5]	210	P daily	55	12	12	13	26	2[e]	10[e]	0.009
Schaake-Koning et al [5]	206	P weekly	55	12	13	13	19	2[e]	10[e]	NS
Trovo et al [15]	146	P daily	45	10	10	14	14	–	–	NS
Jeremic et al [4]	135	CbE daily	69.6 HF	14	22	26	43	9[e]	23[e]	0.02
Jeremic et al [10]	113	CbE weekly	64.8 HF	8	18	25	35	5	21	0.003
Jeremic et al	117	CbE q 3 wks	64.8 HF	8	13	25	27	5	16	NS
Blanke et al [6]	215	P q 3 wks	60–65	10	11	13	18	2	5	NS

[a] $P < 0.05$ when analysis restricted to stage III patients.
[b] $P < 0.05$ if PS 3 patients excluded.
[c] Median TRT dose was 50 Gy but range was 40 to 64 Gy.
[d] 3-year survival.
[e] 4-year survival.

Abbreviations: CAP, cyclophosphamide, adriamycin, cisplatin; CbE, carboplatin, etoposide; EP, etoposide, cisplatin; FVMCAP-5, fluorouracil, vincristine, mitomycin C, cyclophosphamide, doxorubicin, cisplatin; HF, hyperfractionated; MIC, mitomycin, ifosfamide, cisplatin; P, cisplatin; VbP, vinblastine, cisplatin; VdCPU, vindesine, cyclophosphamide, cisplatin, CCNU.

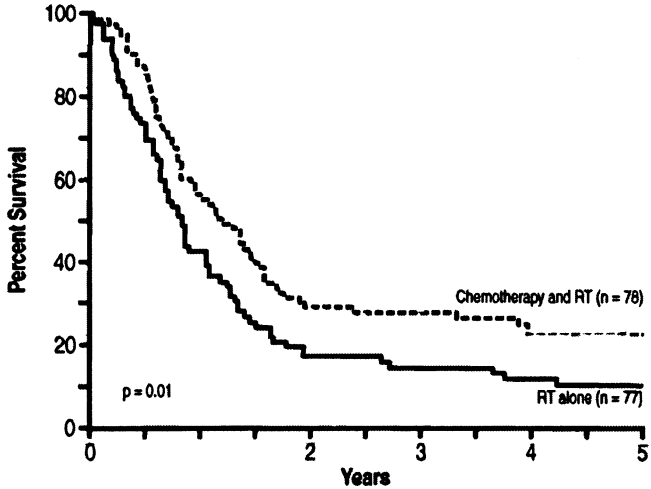

Fig. 1. Survival of patients with stage III NSCLC randomized to radiotherapy (RT) alone (60 Gy) versus two cycles of chemotherapy (cisplatin and vinblastine) and RT (60 Gy). *From* Dillman R, Herndon J, Seagren S. Improved survival in stage III non-small cell lung cancer: seven-year follow-up of Cancer and Leukemia Group B (CALGB) 8433 trial. J Natl Cancer Inst 1996;88:1210–5; public domain.

Concurrent versus sequential chemoradiotherapy

Data from four randomized trials, in which a direct comparison was made between sequential and concurrent chemoradiotherapy, were recently reported (Table 3) [25–28]. In the first reported trial [25], Japanese investigators randomized 320 patients to sequential or concurrent mitomycin, vindesine, and cisplatin. The TRT consisted of a total dose of 56 Gy that was given continuously to patients in the sequential arm and by a split-course schedule in patients in the concurrent arm. Median survival time and 5-year survival rates were statistically superior for the concurrent strategy (Fig. 2). Rates of esophagitis were low and similar on the two arms. Curran

Table 2
Ongoing, randomized phase III cooperative group trials in the United States

Group	Randomization arms
CALGB	Concurrent carboplatin/paclitaxel/TRT (66 Gy) vs Sequential (two cycles) plus concurrent carboplatin/paclitaxel/TRT (66 Gy)
SWOG	Concurrent cisplatin/VP-16/TRT (61 Gy) followed by consolidation docetaxel (three cycles) followed by ZD 1839 or observation
ECOG	Sequential carboplatin/paclitaxel (two cycles) and TRT (60 Gy) with or without thalidomide

Abbreviation: SWOG, Southwest Oncology Group.

Table 3
Randomized trials comparing sequential and concurrent chemoradiotherapy in unresectable stage III NSCLC

				Survival					
				Median (month)		Long-term % (year)		Rates of grade 3/4 esophagitis (%)	
Author [ref]	n	Seq (S) arm	Conc (C) arm	S	C	S	C	S	C
Furuse [25]	320	MVP 56 Gy	MVP 28 Gy→10 day break→28 Gy	13.3 ($P = 0.04$)	16.5	16 (5)	9 (5)	2	3
Curran et al [26]	611	PVb 60 Gy	PVb–60 Gy EP - 69.6 Gy bid	14.6 ($P = 0.04$)	17.1 15.6	18 (3)	25 (3) 23 (3)	4	25 44
Pierre et al [27]	212	PVn 66 Gy	EP 66 Gy	13.8	15.6	24 (2)	35 (2)	0	26
Zatloukal et al [28]	102	PVn 60 Gy	PVn 60 Gy	13.0 ($P = 0.02$)	20.3	12 (2)	42 (2)	4	18

Abbreviations: MVP, mitomycin, vinblastine, cisplatin; PVb, cisplatin, vinblastine; PVn, cisplatin, vinorelbine; EP, etoposide, cisplatin.

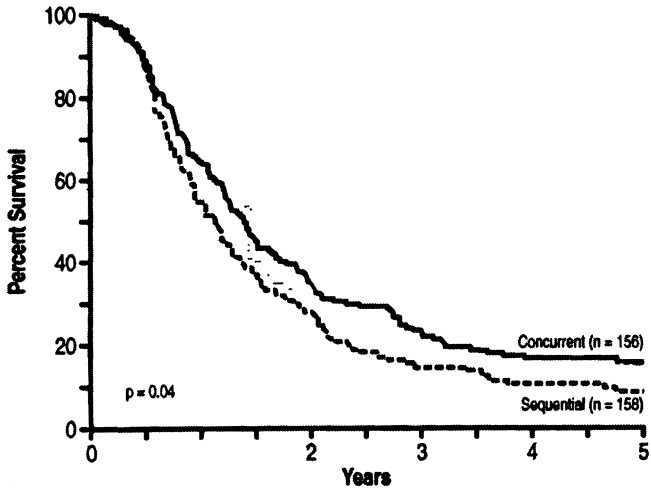

Fig. 2. Survival of patients with stage III NSCLC treated with concurrent versus sequential chemoradiotherapy. *From* Furuse K, for the West Japan Lung Cancer Group. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small cell lung cancer. J Clin Oncol 1999;17:2692–9; with permission.

and colleagues [26] reported the preliminary results of RTOG 94-10 in which this question was also addressed. In that trial, patients received sequential or concurrent cisplatin and vinblastine with 63 Gy of continuous TRT. A third arm used cisplatin and oral etoposide delivered with a hyperfractionated course of TRT to a dose of 69.6 Gy twice a day in a concurrent fashion. There was a statistically significant improvement in median survival for the patients who received the concurrent administration of chemoradiotherapy (see Table 3). In this trial, the rates of severe (grade 3/4) acute esophagitis were substantially higher on the concurrent arm compared with the sequential arm. The third arm, which received concurrent cisplatin/etoposide and hyperfractionated TRT, was numerically but not statistically better than the control arm who received sequential therapy. A third trial that was recently reported by French investigators [27] compared sequential cisplatin/vinorelbine and 66 Gy of TRT with concurrent cisplatin/etoposide and 66 Gy of TRT. Although median and 2-year survival rates were superior for patients who received concurrent therapy (see Table 3), they were not statistically different in this trial which included only 212 patients. Rates of severe (grade 3/4) acute esophagitis were also substantially greater in those who received concurrent therapy. Finally, Zatloukal and colleagues [28] reported a randomized trial that compared sequential and concurrent cisplatin/vinorebline and 60 Gy. The median survival time on the concurrent arm was statistically superior to the sequential arm (see Table 3). Rates of severe esophagitis were also higher on the concurrent arm. These

four trials suggested that concurrent chemoradiotherapy is superior to sequential chemoradiotherapy but at the cost of increased toxicity, mainly esophagitis. Strategies designed to reduce the rate of esophagitis include the use of cytoprotectants such as amifostine [29] or others and improved planning techniques limiting excessive dose to the esophagus. The RTOG is currently conducting a randomized trial that is evaluating the role of amifostine in this setting (RTOG 98-10). Recent data from our institution suggest that limiting the dose of radiation to the esophagus reduces the risk of severe esophagitis [30]. Although the survival benefit of concurrent therapy is modest, it is real; given the number of patients who are diagnosed with unresectable stage III NSCLC annually in the United States, attempts to reduce the overall toxicity of concurrent therapy should be a priority.

New directions in chemoradiotherapy in unresectable stage III NSCLC

As loco-regional and distant control of disease in unresectable stage III NSCLC remains suboptimal, new strategies are being tested in ongoing clinical trials. As discussed earlier, the CALGB is exploring the role of ''induction'' or sequential chemotherapy in addition to the concurrent administration of the same chemotherapy regimen (CALGB 39801) with TRT. The ''induction'' regimen gives systemically active doses for two cycles before concurrent chemoradiotherapy. Both arms use low-dose weekly ''radio-enhancing'' doses of carboplatin and paclitaxel. The extent of the systemic effect of chemotherapy on eradicating occult micrometastatic disease will be defined by this trial. This trial will also partially address the issue of immediate versus delayed TRT. No definitive data exist that address this issue although a small randomized phase II trial, the Locally Advanced Multimodality Protocol, suggested that immediate TRT may be important [31]. This trial must be interpreted with extreme caution as it was not designed to address this issue definitively; there were significant imbalances among the arms in known prognostic factors (weight loss, gender, and performance status) in patients with stage III NSCLC. Without a randomized trial that addresses the optimal timing of TRT, induction and consolidation strategies in combination with concurrent chemoradiotherapy remain options in the curative approach in stage III NSCLC.

Several new agents with significant, single-agent activity in NSCLC have been developed including paclitaxel, docetaxel, vinorelbine, gemcitabine, and irinotecan. Many phase I and II trials investigated the role of these new agents in various approaches combined with TRT [32]. The CALGB completed a large, randomized, phase II trial that evaluated the role of three of these new agents (paclitaxel, vinorelbine, and gemcitabine) in combination with cisplatin and TRT in a sequential and concurrent fashion [33]. Median survival times ranged from 14 to 18 months; myelosuppression and esophagitis are the major toxicities that are experienced in this setting.

The Southwest Oncology Group recently reported the results of SWOG 9504 [34] which added three cycles of consolidation docetaxel following a core regimen of concurrent cisplatin/VP-16 and TRT (61Gy). In a previous trial (SWOG 9019), cisplatin/VP-16 was used as the concurrent and consolidative chemotherapy regimen. The rationale for changing to docetaxel was based on the activity of docetaxel in refractory advanced NSCLC [35–37] and a theoretical hypothesis that using agents with a p53-dependent mechanism of action (eg, cisplatin) followed by an agent with a p53-independent mechanism of action (eg, docetaxel) could lead to enhanced efficacy. This trial (SWOG 9504) included surgically staged IIIB NSCLC patients of which 31% were T_4N_{0-1}. Ninety-seven patients were entered; 83 were determined to be eligible. The toxicity of the consolidation docetaxel consisted mainly of myelosuppression although approximately 10% of patients experienced severe pulmonary toxicity. The survival outcomes were remarkable with a median survival time of 26 months and a 3-year survival of 40% compared with a median survival time of 15 months and a 3-year survival rate of 17% on SWOG 9019. Although the eligibility requirements were similar on the two trials, one must look at comparisons of sequential phase II trials with a doubting eye. Whether the dramatic survival differences that are seen in SWOG 9504 compared with SWOG 9019 are a result of the differences in the consolidative chemotherapy or patient selection issues can only be addressed by a phase III trial. The Hoosier Oncology Group is planning such a trial and is randomizing patients with stage III NSCLC to either observation or docetaxel following concurrent chemoradiotherapy. Unfortunately, the subsequent trial that was launched by SWOG (see Table 2) will not address this issue but will explore the role of ZD1839 (a novel small molecule epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor) as ''maintenance'' therapy following the SWOG 9504 regimen. The role of these new agents is yet to be defined; however, efforts to incorporate these new agents into the chemoradiotherapy paradigm are appropriate. The ECOG is exploring the role of thalidomide in combination with sequential chemoradiotherapy (see Table 2). These trials are currently ongoing with mature results expected in the next 3 to 5 years. Several other new ''targeted'' agents with novel mechanisms of action and radiosensitizing properties are currently being studied in phase I trials with TRT in patients with stage III NSCLC.

The delivery of TRT has remained relatively constant over the past two decades in all of the trials discussed thus far. The dose of TRT has ranged between 56 and 66 Gy in most trials with a few trials using a hyperfractionated approach (generally given twice daily) with doses ranging from 64.8 to 69.6 Gy. In addition, conventional planning techniques use standard chest radiographs as the treatment planning platform. As discussed earlier, this approach has yielded poor local control rates that make cure an impossibility for many patients. Exploring higher total doses of TRT that may yield better local control rates has been limited by the toxicity of such an approach using

conventional treatment planning. The development of three-dimensional treatment planning systems has allowed enhanced tumor targeting by defining clinical tumor volumes using CT-based images. In addition, it has allowed more precise definition of normal intrathoracic structures thereby allowing exclusion of excessive normal tissue from the radiation port and creating the ability to generate interactive radiation treatment plans in individual patients. This ability likely enhances the "therapeutic index" of TRT and more accurately conforms the treatment beam to the three-dimensional aspect of the tumor, hence the term "conformal" TRT. This is a critically important aspect of TRT as it may allow substantially higher total doses to be delivered and chemotherapy to be administered concurrently with less toxicity. Preliminary data has suggested that dose-escalation of TRT is possible. At the University of North Carolina, we have completed a modified phase I/II trial in which we used sequential and concurrent carboplatin/paclitaxel and three-dimensional or conformal radiation therapy planning (TCRT) [38,39]. With this technology, we were able to increase the dose of TCRT from 60 Gy to 74 Gy. The toxicity profile was excellent; only 8% of patients experienced severe esophagitis. The survival outcomes were notable, with a median survival time of 26 months and 2- and 3-year survival rates of 50% and 38%, respectively. We subsequently used TCRT to increase doses beyond 80 Gy with concurrent chemotherapy with acceptable toxicity in this population of patients [40]. Because this technology is more time-consuming and patients are exposed to longer treatment times which extends the time at risk for complications, ultimately to justify the use of such doses in routine practice it must be proven that higher total doses of TCRT result in superior survival outcomes.

Chemotherapy in patients with stage IV NSCLC

Stage IV NSCLC denotes the presence of metastatic disease. Patients with stage IIIB NSCLC, by virtue of malignant pleural/pericardial effusions, and some patients with advanced, palpable supraclavicular adenopathy, however, are generally lumped together with stage IV patients because aggressive local modalities are not appropriate. This section reviews the impact of chemotherapy in good PS patients with stage IIIB/IV NSCLC. PS remains the dominant prognostic factor in this group of patients [41,42]. Most trials have included only patients with ECOG PS of 0 to 1 although some have included ECOG PS 2 patients. The true benefit of chemotherapy in PS 2 patients remains controversial and is discussed later.

The impact that chemotherapy has on survival is best assessed by trials in which some form of chemotherapy was compared with best supportive care (BSC). Table 4 summarizes 18 trials in which this strategy (chemotherapy versus BSC) was evaluated in a randomized trial in patients with advanced NSCLC [8,43–59]. In every trial, the median survival was greater for the chemotherapy arm as compared with BSC; statistical significance was

Table 4
Trials of chemotherapy versus best supportive care in advanced nonsmall cell lung cancer

				Median survival (month)		
Author [ref]	Year	n	Chemotherapy regimen	Chemo	BSC	*P*-value
Non cisplatin-based regimens						
Cormier et al [47]	1982	39	MACC	7.0	2.5	0.0005
Bucchieri et al [44]	1990	175	MACC	7.5	4.6	0.01
Cisplatin-based regimens						
Rapp et al [54]	1988	251	CAP	5.7	3.9	0.05
			VdP	7.5	3.9	0.01
Ganz et al [49]	1989	63	VdP	4.7	3.1	NS
Quoix et al [52]	1991	49	VdP	6.5	2.4	0.001
Woods et al [59]	1990	201	VdP	6.2	3.9	NS
Cellarino et al [46]	1991	128	CErP↔MxEU	7.9	4.9	NS
Kaasa et al [51]	1991	87	EP	5.0	3.7	NS
Cartei et al [45]	1993	102	MCP	8.5	4.0	0.0001
Helsing et al [50]	1998	48	EC	6.7	2.6	0.003
Thongprasert et al [58]	1999	287	IErP/MVbP	6.0	2.5	0.006
Cullen et al [8]	1999	351	MIP	6.7	4.8	0.03
Stephens et al [56]	2002	725	CBC	7.7	5.7	0.0015
New single agents						
Crawford et al [48]	1996	216	Vinorelbine	7.0	5.1	0.03
Anderson et al [43]	2000	299	Gemcitabine	6.1	6.0	NS
ELVIS [57]	1999	171	Vinorelbine	6.5	4.9	0.03
Ranson et al [53]	2000	157	Paclitaxel	6.8	4.8	<0.05
Roszkowski et al [55]	2000	207	Docetaxel	6.0	4.6	<0.05

Abbreviations: CBC, cisplatin-based chemotherapy; CErP↔MxEU-cyclophosphamide, epirubicin, cisplatin→BP-etoposide, cisplatin; EC, etoposide, carboplatin; IErP/MVbP, ifosfamide, epirubicin, cisplatin/mitomycin, vinblastine, cisplatin; MACC, methotrexate, adriamycin, cyclophosphamide, CCNU; MCP, mitomycin, cyclophosphamide, cisplatin; MIP, mitomycin, ifosfamide, cisplatin; VdP, vindesine, cisplatin.

reached in 13 of the 18 trials. Four meta-analyses have been published that examined the effect of treatment versus BSC in patients with advanced NSCLC [23,60–62]. Although the methodology differed among the four meta-analyses, all were consistent in their conclusion that chemotherapy improved survival in patients with advanced NSCLC.

In addition to its survival effect, chemotherapy can palliate symptoms. Table 5 summarizes several trials that documented symptom-relief in patients receiving chemotherapy [63–69]. Disease-specific and disease-nonspecific symptoms may be palliated as a result of treatment. In trials that used dedicated quality-of-life instruments [8,57,58], patients with advanced stage IIIB/IV NSCLC consistently reported improved QOL on chemotherapy compared with BSC.

Breathnach and colleagues [70] reviewed 22 years of phase III trials that evaluated chemotherapy in patients with advanced NSCLC. In 33 randomized trials between 1973 and 1994, only five showed a significant difference in survival. There was a median prolongation of survival of 2

Table 5
Relief of symptoms by chemotherapy in patients with advanced nonsmall cell lung cancer

Author [ref]	Ellis et al [64]	Cullen et al [63]	Osoba et al [67]	Tummarello et al [69]	Fernandez et al [65]	Hardy et al [66]	Thatcher et al [68]
n	120	74	53	46	31	24	NR
Regimen used	MVbP	MIP	BEP	MVbP	PVbMVI	MVbP	Gemcitabine
Objective response rate (%)	32	56	44	33	42	21	20
Median survival (month)	5.0	9.8	5.0	6.5	–	6	8.1–9.2
Symptom improvement (%)[a]							
Cough	66	70	68	40	45	71	44
Hemoptysis	–	92	78	100	91	–	63
Pain	60	77	68	39	47	63	32
Dyspnea	59	46	31	66	78	65	26
Weight loss	–	–	44	30	–	–	–
Anorexia	–	58	–	–	50	–	29
Malaise	53	–	53	62	–	–	–

[a] Percentage of patients with a specific symptom who had relief or improvement in this symptom with treatment. NR – not reported.

From Socinski MA. Chemotherapy for stage IV nonsmall cell lung cancer. Diagnosis and treatment of lung cancer, an evidence based guide for the practicing clinician. Philadelphia: WB saunders; 2001. p. 307–25; with permission.

Abbreviations: MVbP, mitomycin, vinblastine, cisplatin; MIP, mitomycin, ifosfamide, cisplatin; BEP, bleomycin, etoposide, cisplatin; PVbMVI, cisplatin, vinblastine, mitomycin, vincristine, ifosfamide.

months in these positive trials. The trials that were evaluated in this report used nonplatinum-based as well as platinum-based regimens. The chemotherapy agents used, in addition to cisplatin, were vinblastine, vindesine, adriamycin, ifosfamide, mitomycin, cyclophosphamide, and the nitrosoureas. These agents do not have substantial activity in NSCLC (single agent response rate <15%) and are not used in modern-day regimens. Since 1994, several agents with substantial activity (single agent response rates >20%) have been developed which include paclitaxel, docetaxel, gemcitabine, vinorelbine, and irinotecan. All of these agents have been studied in combination with either cisplatin or carboplatin. The Multidisciplinary Thoracic Oncology Program at the University of North Carolina performed a meta-analysis [71] of the published literature and compared platinum-based regimens, including one of these new agents (third-generation, platinum-based regimen), to an older second-generation, platinum-based regimen (typically using a vinca alkaloid or etoposide). We identified eight trials, that included 3296 patients, that were published since 1994. In our analysis of heterogeneity, the results of the trials were believed to be consistent, allowing a summary analysis. Response rates were improved with the newer regimens (RR 1.80, 95% CI, 1.5–2.15) with an absolute increase of 13%. More importantly, one-year survival was increased with

the newer regimens compared with the older regimens (RR 1.14, 95% CI, 1.01–1.29). There was an absolute increase in survival of 4% at 1 year. There was no difference in the rates of treatment-related deaths when the newer, third-generation regimens were compared with the older, second-generation regimens. This analysis suggests that there has been a significant, albeit small, improvement in survival associated with the use of modern-day regimens.

Since 1999, several trials [72–77] were reported in which the new, third-generation, platinum-based regimens were compared in randomized, phase III trials (Table 6). The Southwest Oncology Group compared cisplatin/vinorelbine to carboplatin/paclitaxel and found response rates, QOL, median, and overall survival to be equivalent [73]. The Eastern Cooperative Oncology Group compared cisplatin/paclitaxel to carboplatin/paclitaxel, cisplatin/docetaxel, and cisplatin/gemcitabine [76]. There were no significant differences in response rates, median, or overall survival. The Italian Lung Cancer Study Group (ILCSG) compared cisplatin/vinorelbine, cisplatin/gemcitabine, and carboplatin/paclitaxel [75]. Once again, no significant differences in response rates, median, or overall survival were noted. A large, international trial [74] compared cisplatin/vinorelbine to either cisplatin/docetaxel or carboplatin/docetaxel. The trial was not designed to compare the cisplatin/docetaxel arm to the carboplatin/docetaxel arm. There was a significant survival advantage for the cisplatin/docetaxel arm as compared with the cisplatin/vinorelbine arm. No significant difference was seen between

Table 6
Randomized phase III trials of new regimens in advanced NSCLC

Group [ref]	n	% Stage IV	Regimens	RR (%)	Survival	
					Median (month)	1-year (%)
SWOG [73]	408	92	Carbo/paclitaxel	27	8.0	36
			Cis/vinorelbine	27	8.0	33
ECOG [76]	1155	87	Cis/paclitaxel	21	7.8	31
			Carbo/paclitaxel	17	8.1	34
			Cis/docetaxel	17	7.4	31
			Cis/gemcitabine	22	8.1	36
ILCSG [75]	612		Cis/vinorelbine	31	9.5	37
			Cis/gemcitabine	30	9.8	37
			Carbo/paclitaxel	32	9.9	43
International [74]	1220	67	Cis/vinorelbine	NR	10.0	42
			Cis/docetaxel	NR	10.9	47
			Carbo/docetaxel	NR	9.1	38
SLCG [72]	562	79	Cis/gemcitabine	43	8.7	35
			Cis/gemcitabine/vino	38	7.9	31
			Gem/vino→ifos/vino	26	8.1	35
EORTC [77]	480	79	Cis/gemcitabine	37	8.8	33
			Cis/paclitaxel	31	8.1	36
			Paclitaxel/gemcitabine	27	6.9	27

Abbreviations: Carbo, carboplatin; Cis, cisplatin; Vino, vinorelbine; ifos, ifosfamide.

the cisplatin/vinorelbine arm and the carboplatin/docetaxel arm. Two recent trials evaluated the role of triplet combinations as well as nonplatinum-based doublets. In recent, randomized, phase II/III trials [78–80], nonplatinum-based doublets were equivalent to platinum-based doublets; however, the phase II experience is not meant to be comparative between the regimens. The European Organization for the Research and Treatment of Cancer (EORTC) compared cisplatin/gemcitabine to cisplatin/paclitaxel and paclitaxel/gemcitabine [77]. There was no significant difference between the two platinum-based arms. The survival of the patients who received paclitaxel/gemcitabine was disappointingly low (median survival time of 6.9 months and 1-year survival of 27%); this suggested that the platinums should remain an integral part of the regimen in patients with advanced NSCLC. The Spanish Lung Cancer Group (SLCG) [72] compared cisplatin/gemcitabine to the triplet combination of cisplatin/gemcitabine/vinorelbine as well as a sequential strategy of nonplatinum-based doublets. No advantage was apparent for the triplet combination or the nonplatinum-based doublets that were used in a sequential fashion. These six trials that were reported over the last 3 years suggested that platinum-based doublets, which include any of the new, third generation agents, represent ''standard of care'' regimens that yield equivalent response and survival rates in patients with advanced stage IIIB/IV NSCLC.

Three recent trials [81–83] addressed the issue of whether the new agents used alone were equivalent to the same agent combined with a platinum. The CALGB compared paclitaxel to carboplatin/paclitaxel in 584 patients with advanced NSCLC [82]. The median survival, as well as time-to-progression, significantly favored the combination arm. One-year survival, however, was not superior. Significantly more patients who were randomized to paclitaxel alone received second-line treatment which included platinum-based combinations; this may have impacted the 1-year survival rate. The Swedish Lung Cancer Stage Group [83] randomized 332 patients with advanced NSCLC to either gemcitabine or carboplatin/gemcitabine. Survival was significantly improved for those patients who were randomized to the combination. Patients who were randomized to single-agent gemcitabine were not allowed to receive second-line, platinum-based treatment. In a smaller trial, the Greek Cooperative Group for Lung Cancer [81] randomized 307 patients to docetaxel or cisplatin/docetaxel. Although survival outcomes were numerically superior for the combination, the differences observed did not achieve statistical significance. When taken together, these three trials suggest that platinum-based combination regimens that use the new agents should remain the standard of care and the platform upon which new targeted agents should be evaluated in the phase III setting.

Treatment of the elderly

It is estimated from the National Cancer Database that 30% to 40% of patients are 70 years of age or older when they are diagnosed with NSCLC

[84]. With age and a significant smoking history present in most of these patients, comorbid conditions are common and may compromise performance status or complicate safe administration of chemotherapy.

Several studies specifically addressed the treatment of the elderly with advanced NSCLC (Table 7). In a landmark trial [57], elderly patients (defined as $\geq$70 years) with advanced NSCLC were randomized to BSC or vinorelbine. The patients who received vinorelbine had superior survival outcomes and superior QOL compared with patients who received BSC. A subsequent trial [85] evaluated the combination of vinorelbine/gemcitabine compared with vinorelbine alone and suggested a survival benefit to the combination. The survival of the patients who received vinorelbine alone was similar to the survival of the patients who received BSC on the previous study, however. A third trial [86] compared vinorelbine to gemcitabine as well as the combination of vinorelbine/gemcitabine. No significant differences among the arms were noted in response rates or survival. These trials support the routine use of chemotherapy in elderly patients with good PS and provide several options regarding the choice of therapy. In addition, several analyses of platinum-based regimens used in the United States, including cisplatin/paclitaxel, carboplatin/paclitaxel, cisplatin/vinorelbine, and cisplatin/etoposide, have been reported [87–89]. These analyses suggested that the elderly (defined as $\geq$65 to 70 years) who received platinum-based therapy derived similar survival benefits when compared with younger patients. When carboplatin-based regimens were evaluated, no differences in toxicity patterns, based on age, were apparent [87,88]; this may or may not be true of cisplatin-based regimens [88,89]. Single-agents, as well as platinum-based regimens, are therapeutic options for fit, elderly patients with advanced NSCLC.

Treatment of patients with poor performance status

The observation that patients with poor PS experience more toxicity and have poorer survival outcomes was documented in the 1980s by the ECOG

Table 7
Randomized trials in the elderly with advanced NSCLC

				Survival		
Author	Regimen	n	RR (%)	Med (month)	1-year (%)	*P* value
ELVIS [57]	Vinorelbine	161	20	6.5	32	0.03
	BSC		–	4.9	14	
Frasci et al [85]	Vinorelbine	120	15	4.2	13	<0.01
	Vino/gemcitabine		22	6.8	32	
Gridelli et al [86]	Vinorelbine	700	19	8.6	41	
	Gemcitabine		17	6.5	26	NS
	Vino/gemcitabine		20	7.5	31	

[41]. In a retrospective review of prospective, cisplatin-based trials, the median survival time of PS 2 patients was 3.3 months compared with median survival times of 6.4 months and 9.4 months for PS 1 and PS 0 patients, respectively ($P < 0.05$). The European Lung Cancer Working Party analyzed 1052 patients who received cisplatin-based therapy [90] and documented a 3-month difference in median survival times between patients with good PS and patients with poor PS ($P < 0.0001$). Recent trials showed that PS 2 patients have poorer survival outcomes. In the EORTC trial [77], the median survival time of PS 2 patients was 3.3 months compared with 8.6 month for the PS 0–1 patients. In the SLCG trial [72], the median survival time of the PS 2 patients was 4.7 months compared with 9.1 months for PS 0–1 patients. In a retrospective analysis of the ILCSG trial [91], the median survival of PS 2 patients was 4.6 months compared with 10.1 months in the PS 0–1 patients. In addition to the poorer survival, the rates of toxicity that were experienced in this group of patients is also a concern. A recent report summarized the outcome of PS 2 patients with advanced NSCLC who received therapy on ECOG 1594 [76]. This was a four-arm trial that compared cisplatin/paclitaxel to cisplatin/gemcitabine, cisplatin/docetaxel, and carboplatin/paclitaxel. The Data Monitoring Committee of the ECOG discontinued accrual of PS 2 patients after an analysis in 66 patients revealed 5 (7.6%) deaths on study. The rate of severe toxicity (grade 3–4) in the PS 2 patients ranged from 71% to 90% for the cisplatin-based regimens compared with 60% for the carboplatin/paclitaxel regimen ($P = 0.0032$). A lower incidence of severe neutropenia and less nausea, vomiting, and diarrhea accounted for the differences. The overall median survival time and 1-year survival were 4.1 months and 19.1%, respectively. Given these data, the most appropriate strategy to pursue in the PS 2 patient remains undefined. Use of the less toxic platinum analogue, carboplatin, can reduce toxicity but rates of severe toxicity are still approximately 60%. The use of single-agent therapy is attractive as it reduces the risk of toxicity and may yield equivalent survival rates in this population. This issue is complicated by the observation in the recent CALGB trial [82] that PS 2 patients who received carboplatin/paclitaxel had a survival advantage compared with those who received paclitaxel alone in a planned, prospective, subset analysis. The continuing evaluation of new strategies in PS 2 patients is warranted; it should be kept in mind that this population has an increased risk of experiencing excessive toxicity which may negatively impact on an individual patient's quality of life. The overall survival of PS 2 patients is poor; future therapeutic interventions must clearly document a survival improvement unless the palliative benefit is compelling and toxicity is minimal.

Duration of therapy in patients with advanced NSCLC

Given the noncurative nature of chemotherapy in patients with advanced NSCLC, another issue that deserves a brief mention is the optimal duration

of therapy. The optimal duration of first-line therapy in patients with advanced NSCLC was addressed in three trials [92–94] (Table 8). These trials pursued the following strategies: (1) three versus six cycles of mitomycin, vinblastine, and cisplatin; (2) four cycles versus continuous treatment with carboplatin/paclitaxel; and (3) four cycles of mitomycin, ifosfamide, and cisplatin followed by either observation or single agent vinorelbine for four cycles. The three trials are somewhat different in their design but all three are consistent in their conclusion that prolonging therapy beyond three or four cycles does not improve survival. These trials suggested that the survival and palliative effect that chemotherapy has occurs in the first three to four cycles of therapy. In all three trials, prolonging chemotherapy beyond three to four cycles increased the risk of cumulative toxicities. Given this, brief durations of first-line therapy are appropriate, thereby maximizing the "therapeutic index" of chemotherapy.

Second-line treatment of advanced NSCLC

First-line therapy is not curative in patients with advanced NSCLC; all patients will experience progressive disease unless they have a fatal disease-related complication or comorbid event. In recent phase III trials, the median time to tumor progression was 3 to 5 months [72–77]. In many cases, progression of disease is determined while the patient still has a good performance status, and patients, in general, want further therapy. In recent trials of first-line therapy, a minority of patients received second-line therapy. In our experience at the University of North Carolina, approximately 40% of patients with advanced stage IIIB/IV NSCLC received second-line therapy [94,95]. Until recently, the role of second-line therapy was uncertain; however, two recent, phase III trials [36,38] suggested a clear benefit from therapy (Table 9). In the "purest" of the two trials, Shepherd and colleagues [38] randomized patients who had progressed after receiving first-line platinum-based therapy to receive either

Table 8
Trials addressing the optimal duration of therapy in patients with advanced NSCLC

Author [ref]	n	Randomization	Outcome
Smith et al [93]		Three vs six cycles of MVP	No benefit in RR, TTP, symptom relief, or survival for six cycles vs three cycles
DePierre et al [92]		Four cycles of MIP, then observation vs vinorelbine	No benefit in survival for vinorelbine vs observation
Socinski et al [94]		Four cycles vs continuous therapy with carboplatin/paclitaxel	No benefit in RR, QOL, or survival for therapy beyond four cycles

Table 9
Randomized trials of second-line docetaxel in stage IIIB/IV NSCLC patients previously treated with platinum-based chemotherapy

			Survival	
Treatment arm	n	RR (%)	Med (month)	1-year (%)
Docetaxel 100 mg/m^2	49	6.3	5.9	19
Docetaxel 75 mg/m^2	55	5.5	7.5[a]	37[a]
Docetaxel 75 + 100 mg/m^2	104	7.1	7.0[b]	29[b]
BSC	100	–	4.6	19
Docetaxel 100 mg/m^2	125	12[c]	5.5	21
Docetaxel 75 mg/m^2	125	7.5[c]	5.7	32[d]
Vinorelbine/Ifosfamide	123	1	5.6	19

[a] $P = 0.03$ for docetaxel 75 mg/m^2 versus BSC, log rank test.
[b] $P = 0.047$ for both docetaxel arms versus BSC.
[c] $P < 0.05$ for response rate of either dose of docetaxel versus either vinorelbine (n = 89) or ifosfamide (n = 34).
[d] $P = 0.025$ versus vinorelbine/ifosfamide, chi-square test.

single-agent docetaxel or BSC. The choice of docetaxel was based on favorable results with this agent in the second-line setting in phase II trials [36,96]. Patients who were randomized on the Shepherd trial were not permitted to have had first-line taxane therapy. In the original design, 100 mg/m^2 of docetaxel was administered every 3 weeks which proved to be too toxic and could not be administered in this setting as patients received only a median of two cycles. The dose was subsequently changed to 75 mg/m^2 and a median of four cycles was delivered. An evaluation of the survival of all patients revealed a significant survival advantage for treated patients versus those who were randomized to BSC (Fig. 3). The median survival time and 1-year survival rates were 4.6 months and 19% and 7.0 months and 19% for BSC and docetaxel, respectively ($P = 0.047$). A companion analysis of palliative endpoints suggested improvement in disease-related symptoms, including pain [97]. Toxicity at the 75 mg/m^2 dose of docetaxel was acceptable with grade 4 neutropenia occurring in 67% of patients; 2% of patients developed febrile neutropenia. Nonhematologic toxicity consisted mainly of asthenia and pulmonary toxicity. A second trial [36] randomized patients who had progressed after first-line, platinum-based chemotherapy to two dose levels of docetaxel (100 mg/m^2 and 75 mg/m^2) and either vinorelbine or ifosfamide. Median survival times were similar for all three arms (5.5–5.7 months); however, 1-year survival was superior for the arm that received 75 mg/m^2 of docetaxel (32%) compared with the arm that received 100 mg/m^2 of docetaxel (21%) and the arm that received vinorelbine/ifosfamide (19%) ($P = 0.025$ docetaxel 75 vs vinorelbine/ifosfamide, chi-square test). Taken together, these two trials suggest that benefit can be achieved in the second-line setting when patients progress following first-line, platinum-based regimens. Although the "proof of concept" trials were done with docetaxel, it is likely that other agents

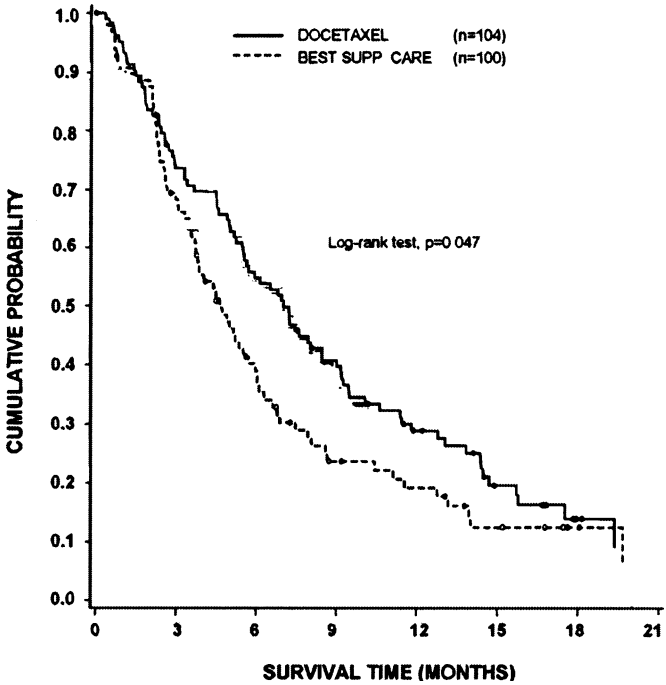

Fig. 3. Survival of patients with stage IV NCSLC previously treated with platinum-based regimens randomized to single-agent docetaxel versus best supportive care (BSC). *From* Shepherd F, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095–103; with permission.

(gemcitabine, paclitaxel, and others) also have activity [95,96,98,99] in selected patients. Although prognostic factors that predict benefit in the second-line setting have not been clearly defined, intuitively it seems that response to the first-line regimen, a prolonged progression-free interval, and performance status at the time of progression would identify patients who are more likely to benefit from second-line therapy. After patients complete first-line therapy they should be followed closely for progression given the possibility that more therapy can have a survival and palliative effect. The optimal surveillance strategies for these patients have not been defined and probably should be individualized for each patient.

Future directions in advanced stage IIIB/IV NSCLC

The trials that were summarized in Table 6 suggested that the survival outcomes in patients with advanced NSCLC have plateaued and further "rearrangements" of currently available cytotoxic agents are unlikely to

have a significant effect on improving survival. The active cytotoxic agents in common use today exert their effect either on the microtubular apparatus of the neoplastic cell or on DNA synthesis. Although these agents likely represent a necessary component of our therapeutic armamentarium for the foreseeable future, our understanding of the biology of cancer has increased exponentially during the past decade. It is now clear that the neoplastic process is not simply sustained replication [100]. Cancer cells develop mechanisms that allow unopposed growth signal stimulation and escape from the impact of antigrowth signals. Our understanding of the angiogenic pathway and the mechanisms by which a developing cancer sustains angiogenesis and accomplishes access to the vasculature allowing metastases to form has been defined. This understanding has created several new "targeted" agents that have remarkable specificity for the target. Many phase III clinical trials are now underway to explore the efficacy of many new agents in combination with cytotoxic chemotherapy in patients with advanced NSCLC. A few of the agents for which phase III data will be available soon are described below.

The epidermal growth factor receptor is overexpressed in most patients with advanced NSCLC; it likely plays an important role in the pathogenesis of this disease [101]. The EGFR has an external domain (that binds transforming growth factor α as one ligand) as well as an internal domain that possesses tyrosine kinase activity. Signaling from this receptor promotes proliferation of the neoplastic cell and inhibits apoptosis. Given the importance of EGFR in NSCLC, several strategies that are directed at this receptor are under development. ZD1839 is a novel small molecule that potently inhibits the tyrosine kinase activity of EGFR [102]. This orally-administered agent showed activity in phase I and II trials involving patients with refractory advanced NSCLC [103,104]. The principal toxicities of ZD1839 are rash and diarrhea but these are rarely severe. ZD1839 has also been successfully used with combination chemotherapy regimens (carboplatin/paclitaxel and cisplatin/gemcitabine) that are commonly used in patients with advanced NSCLC; it does not seem to alter pharmacokinetic or pharmacodynamic parameters. Two placebo-controlled, phase III trials have been completed in which two dose levels of oral ZD1839 (250 mg and 500 mg) in combination with either carboplatin/paclitaxel or cisplatin/gemcitabine were compared with the chemotherapy combination alone. Both of these trials enrolled slightly more than 1000 patients with advanced stage IIIB/IV NSCLC and will be pivotal in evaluating this new agent's impact on survival in this setting. ZD1839 monotherapy has shown activity in the second-line and third-line setting in patients with advanced NSCLC and may soon be a therapeutic option in the palliative treatment of refractory disease [103,104]. Other small molecule tyrosine kinase inhibitors (eg, OSI-774 [105]) and monoclonal antibodies directed at the EGFR are currently being tested in patients with advanced NSCLC in the first-line and second-line setting.

Matrix metalloproteinases (MMP) are a family of zinc-containing enzymes that degrade extracellular matrix proteins and have been implicated in angiogenesis and tumor progression [106]. Matrix metalloproteinases inhibitors (MMPI) were evaluated in phase III trials in patients with advanced NSCLC [107,108] and small cell lung cancer (SCLC) [109]. Prinomastat was tested in patients with NSCLC whereas marimastat was evaluated in patients with SCLC. Neither phase III trial showed a survival benefit; toxicity profiles showed substantial musculoskeletal toxicity from both MMPIs. The toxicity of the MMPIs may be secondary to their broad activity and inhibition of a family of enzymes called sheddases. ''Second-generation'' MMPIs have been developed that inhibit only MMP and spare sheddases; this results in no dose-limiting or efficacy-limiting musculoskeletal toxicity [106]. One such MMPI is BMS-275291, which is currently being tested in a phase III trial in combination with carboplatin/paclitaxel. The results from this trial are not yet available.

Protein kinase C-α (PKC-α) is a critical enzyme in the malignant process that facilitates proliferation and possesses antiapoptotic properties [110]. This enzyme is also abnormally expressed in many human malignancies. In a new pharmacologic approach, the antisense approach, perfectly matched oligonucleotides prevent translation of a protein from its mRNA. LY900003 (formerly known as ISIS 3521) is a novel 20-base oligonucleotide that targets the 3′ end of human PKC-α mRNA. In preclinical models, LY900003 suppresses PKC-α mRNA and protein in tumor cell lines and in xenograft models and is additive with various chemotherapeutic agents in tumor xenograft models. Phase I/II testing of LY900003, in combination with carboplatin/paclitaxel, revealed no significant changes in toxicity profiles of the regimen and yielded promising median and 1-year survival times [111]. A phase III trial was completed in which 600 patients with advanced NSCLC were randomized to carboplatin/paclitaxel with or without a 14-day infusion of LY900003. Results should be available in early 2003.

Angiogenesis is a critical aspect of the development and propagation of any malignancy. Vascular endothelial growth factor (VEGF) is an important mediator of this process and promotes survival and proliferation of endothelial cells [112]. VEGF gene expression is increased in the majority of human tumors compared with the surrounding normal tissue. Antibodies and small molecule inhibitors directed at the VEGF pathway have been defined and are currently under clinical evaluation. A recombinant humanized version of the murine antibody, rhuMAb-VEGF (anti-VEGF) was produced; safe dosing and tolerability has been established in humans. A recent trial in 99 patients with advanced stage IIIB/IV NSCLC combined anti-VEGF at two dose levels with carboplatin/paclitaxel and also compared carboplatin/paclitaxel alone followed by anti-VEGF at the time of progression [113]. Response rates were generally higher for patients who received anti-VEGF in combination with carboplatin/paclitaxel compared

with those patients who received carboplatin/paclitaxel alone. Median survival times ranged from approximately 12 months to 14 months for all three arms; this was promising. One worrisome toxicity, life-threatening hemoptysis, occurred in 6 of 66 patients (9%) who were treated with anti-VEGF; it occurred predominantly in those patients with squamous cell histology. In a separate analyses of the patients with nonsquamous cell histology, the median survival times ranged from 12.3 months for the patients who received carboplatin/paclitaxel followed by anti-VEGF to 17.9 months for those who received carboplatin/paclitaxel and the higher dose of anti-VEGF. Because of these optimistic results, the ECOG has begun a randomized phase III trial to compare carboplatin/paclitaxel with and without anti-VEGF. This trial is restricted to patients with non-squamous histology because of the apparent risk of life-threatening hemoptysis that

Box 1. New "targeted" agents in advanced NSCLC.

Signal transduction inhibitors/cell-cycle inhibitors
Flavopiridol
Farnesyl transferase inhibitors
Retinoids
UCN-101

Angiogenesis inhibitors
anti-VEGF
ZD6474
Ly317615T
TNP-470

Anti-EGFR
ZD1839 (Iressa)
C225 (Erbitux)
OSI-774 (Tarceva)
ABX-EGF
CI-1033

Gene therapy
Wild type p53
Antisenses - PKC, C-myc

Vaccines
Tumor cells
Peptides
Dendritic cells
Viral vaccines

was observed in the population with squamous cell histology. This trial will be closely monitored given the uncertain risk of this toxicity.

Box 1 summarizes many of the new classes of targeted agents that currently under study in patients with advanced NSCLC. These agents have target specificity and are directed at new pathways defined by understanding the biology of lung cancer. In many cases, the new agents have additive or synergistic interaction with various chemotherapeutic agents, as well as radiotherapy. Tolerability and feasibility studies of many of these agents are underway in patients with lung cancer. The ultimate role that these agents will play in the therapeutic approach to advanced NSCLC will be defined in carefully designed and conducted clinical trials.

Summary

Modern platinum-based combination chemotherapy has played a major role in the therapeutic approach to unresectable stage III and IV NSCLC. Randomized phase III trials clearly documented a survival as well as palliative benefit to treatment in patients with stage IV NSCLC who have a good PS (PS 0–1). The optimal therapeutic approach in patients with poor PS (PS 2) has not yet been defined. Recent trials that focused on the elderly suggested that they receive benefits from chemotherapy that are similar to their younger counterparts. The benefit from chemotherapy seems to occur early (initial 3 to 4 cycles) and prolonged therapy is not indicated. Second-line therapy that is administered upon progression was shown to provide survival and palliative benefits. In unresectable stage III NSCLC, the addition of chemotherapy to TRT improves long-term survival and has the potential to cure a minority of patients. Although sequential and concurrent chemoradiotherapy approaches have improved survival in phase III trials, concurrent strategies seem superior in comparative trials. New techniques in radiation therapy, such as three-dimensional treatment planning, may allow safer administration of both modalities concurrently and allow higher doses of TRT to be delivered. In unresectable stage III and stage IV NSCLC, the role of the new "targeted" therapies is currently being defined in several randomized, phase III trials. It is imperative that physicians who care for patients with advanced NSCLC be aware of these trials and attempt to enroll their patients, if possible. It is only through the successful and timely completion of well-designed clinical trials that we will advance our knowledge of improved treatment options for our patients with this disease.

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