THERAPY FOR STAGE IIIB AND STAGE IV NON–SMALL CELL LUNG CANCER

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Complete surgical resection remains the cornerstone of treatment for non-small cell lung cancer (NSCLC). Due to the presence of advanced disease at diagnosis or comorbid illness, however, curative resection is feasible in fewer than one third of these patients. For patients not amenable to surgery, the goal of therapy is to control the tumor locally and at distant sites. Recent clinical trials have tested new chemotherapeutic regimens, novel radiation therapy (RT) techniques, and combined modality approaches. As a result, RT combined with chemotherapy is recognized as the current standard of care for selected patients with unresectable, nonmetastatic NSCLC. In addition, novel molecular targets are being identified, and modulators of these targets are being evaluated in clinical trials. Preliminary reports of these drugs, which include inhibitors of the cell cycle, signal transduction, and angiogenesis, demonstrate promising activity. The authors review the results of these recent trials and attempt to define the current status of chemotherapy and RT in the treatment of advanced NSCLC.

STAGE IIIB AND UNRESECTABLE IIIADISEASE

Role of Radiotherapy

Primary Radiotherapy

At the time of diagnosis, approximately one third of all patients with NSCLC have detectable disease confined to the thorax that is too advanced for curative surgery. In the United States, this represents an estimated 50,000 new cases annually. Radiation has been standard treatment for unresectable NSCLC since the 1940s. With definitive radiation alone, 5-year survival rates do not exceed 10%.[41, 90, 103, 145]

Early studies investigating whether RT prolongs survival were inconclusive because of methodologic problems.[55, 163] Based on Radiation Therapy Oncology Group (RTOG) protocol 73–01, the standard curative regimen used in North America is 50 to 60 Gy delivered in 2-Gy fractions over 5 to 6 weeks.[146, 147] In the RTOG study, a significant dose-response for local control was seen for tumors 6 cm or less, with response rates of 61% to 66% with 50 to 60 Gy, versus 48% with 40 Gy. A durable *dose–survival* relationship, however, was not demonstrated for the higher doses of radiation given that the survival curves merged by 3 years and survival at 5 years were the same in all arms (6%).[145] Two prospective randomized trials since have compared this RT schedule with chemotherapy.[103, 105] Crossover was allowed in both of these trials. No advantage to early introduction of definitive RT was demonstrated.

Intrathoracic failure following primary radiotherapy is a major obstacle to achieving meaningful survival for patients with NSCLC.[56, 145] When response was assessed by bronchoscopy, the complete response rate at 1 year following conventional radiotherapy was only 17%.[117] High doses[108, 124, 146] and uninterrupted, timely delivery of radiation[40, 65] seem to be important determinants of lo-

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Table 1. VARIOUS STRATEGIES IN RADIOTHERAPY

References	Type of RT	RT Regimen (Total Dose/Fraction Dose/Duration)	Evaluable Patients	GR 3–4 Toxicity (%)		Survival 3-year (%)
				*Esoph**	*Lung†*	
RTOG 73–01[147]	Standard	60 Gy/2 Gy/6 weeks	86	2	7	5
RTOG 73–02[187]	Palliative	30 Gy/3 Gy/2 weeks	98	1	1	0
Holsti et al[98]	Split-course	55 Gy/2 Gy/7–8 weeks split by a 2–3 week rest period	205	N/R	N/R	7
Intergroup[175, 177]	HFX	69.6 Gy/1.2 Gy bid/6 weeks	149	1	20	14
Saunders et al[173, 174]	CHART	54 Gy/1.5 Gy tid/12 days including weekends	338	19	16	20
RTOG 92–05[95]	HART	79.2 Gy/1.1 Gy tid/5 weeks excluding weekends	35	9	9	18
Hayman et al[93]	3D CRT	63-84 Gy/2.1 Gy/variable	76	6	2	14

RTOG = Radiation Therapy Oncology Group; Intergroup = RTOG 88–08/Eastern Cooperative Oncology Group (ECOG) 4588/Southwestern Oncology Group (SWOG) 8992; RT = radiotherapy; HFX = hyperfractionated; CHART = continuous hyperfractionated accelerated radiotherapy; HART = hyperfractionated accelerated radiotherapy; 3D CRT = three-dimensional conformal radiotherapy; bid = twice daily; tid = three times daily; N/R = not reported.

*Esophagitis: grade 3 = dysphagia requiring intravenous hydration, grade 4 = complete obstruction requiring parenteral nutritional support.

†Pulmonary fibrosis: grade 3 = radiographic changes and requiring oxygen, grade 4 = radiographic changes and requiring assisted ventilation.

coregional control and survival. An optimal schedule of radiation for the management of NSCLC remains controversial. The various approaches used in clinical practice are summarized in Table 1.

Conformal Radiotherapy

Escalation of the dose of radiation is limited by normal tissue tolerance. For radiation delivered to the thorax, the severity of lung injury best correlates with the volume of total lung receiving more than 20 Gy, designated as V_{20}. In a retrospective review of studies in which the overall incidence of pneumonitis ranged from 19% to 30%, the incidence of grade 3 or higher pneumonitis was zero when V_{20} was less than 25%, whereas all cases of severe pneumonitis occurred at V_{20} equal to or greater than 32% and all fatal cases, at V_{20} greater than 37%.[83] The V_{20} parameter is easy to define, and its use in predicting the risk for pneumonitis is being evaluated prospectively by RTOG 93–11, a large conformal dose-escalation trial.[82]

Three-dimensional conformal RT (3D CRT) is a strategy based on more precise computer-assisted treatment planning and dose delivery, whereby the ratio of radiation delivered to the tumor volume relative to the surrounding normal tissues is enhanced.[196] The University of Michigan has been using 3D CRT since 1985 and, in a review of their dose-escalation studies, a nonstatistically significant trend toward longer local progression-free survival (LPFS) was observed for patients treated with more than 70 Gy compared with less than 70 Gy.[128] With tumor doses of more than 70 Gy, the estimated LPFS was 81% at 12 months but dropped to 38% by 30 months. To achieve 50% LPFS at 30 months, it is estimated that doses in excess of 80 Gy will be necessary.[128]

Several clinical trials have demonstrated the safety of delivering 70 to 100 Gy using 3D CRT.[84, 93, 162, 186] Using a stereotactic approach, a Japanese group has treated tumors up to 4.5 cm in size with schedules ranging from 30 Gy in divided doses over 1 week to 75 Gy in divided doses over 3 weeks and achieved a 96% LPFS with a median follow-up of 11 months.[200] Omission of elective mediastinal irradiation is necessary if doses are escalated beyond 60 Gy. A randomized comparison has yet to test conformal radiotherapy against the conventional two-dimensional (2D) planning practice. The optimal dose and the optimal size of the treatment field still are being defined. Combination with surgery, modern chemotherapy,[30] or accelerated or hyperfractionated RT[127] is likely to be necessary to realize the full potential of 3D CRT.

Altered Fractionation Radiotherapy

The standard RT schedule is to deliver 2-Gy fractions once daily, 5 days per week, over 5 to 6 weeks. Schedules with more than once-daily fractions are termed *hyperfractionated*, and schedules that deliver fewer fractions are described as *hypofractionated*. The use of hypofractionated radiation is restricted to palliative care.[39]

Hyperfractionation. A hyperfractionated regimen has the theoretic advantage of delivering a higher total dose of radiation without increasing treatment time or late normal tissue toxicity. Radiation Therapy Oncology Group 83–11 was a phase I and II study of hyperfractionated RT, evaluating total doses ranging from 60 to 79.2 Gy given as 1.2-Gy fractions twice daily.[38] A subset of patients with minimal weight loss, high performance status, and lack of supraclavicular adenopathy benefited optimally from 69.6 Gy. The 2-year survival for this favorable subset was 29%, compared with 10% observed among matched patients treated

with standard 60 Gy in RTOG 83–21. Unfortunately, this apparent survival advantage did not persist beyond 3 years. Furthermore, a subsequent intergroup trial could not confirm the superiority of hyperfractionation despite a 20% to 30% increase in the total dose; 5-year survival rates for the standard RT and hyperfractionated RT arms were 5% and 6%, respectively.[175, 177]

Accelerated Hyperfractionation. The main aim of acceleration is to limit the rapid repopulation of tumor cells by shortening the interfraction interval and the overall treatment time. Hyperfractionated acceleration, by using smaller fraction sizes, allows for dose intensification while sparing late-responding tissues. In 1986, a group of investigators from England reported a small study of continuous hyperfractionated accelerated radiotherapy termed *CHART*.[172] This regimen consisted of 36 fractions of 1.5 Gy given three times daily over 12 consecutive days to a total dose of 54 Gy.[171] This effort later was expanded to a multicenter randomized trial comparing CHART to the standard 60 Gy/30 fraction/6-week regimen in locally advanced NSCLC.[174] Three-year survival was 20% with CHART versus 13% with standard radiotherapy.[173] This statistically superior survival outcome was restricted to patients with squamous cell histology, a subgroup comprising approximately 80% of this study population. The survival rates for nonsquamous subtypes trended in favor of conventional RT over CHART. Local control, despite being improved with CHART, was still dismal, at 13% at 3 years, even for patients with squamous cell histology.

The major acute toxicity, occurring sooner and more frequently with CHART, was esophagitis. The incidence of dysphagia impairing oral intake was 19% versus 3%, but this difference did not persist beyond 90 days. At 2 years, radiographic evidence of fibrosis was present in about half the patients in both treatment arms, but more patients randomized to CHART—16% versus 4%—required treatment for symptomatic radiation pneumonitis. Neurotoxicity manifested as lower extremity paresthesia on neck flexion (Lhermitte's sign), without the development of radiation myelitis, was observed in 8 of 338 patients treated with CHART.

Because of logistical considerations, this type of hyperfractionated acceleration schedule is unlikely to become common practice within the United States. Radiation Therapy Oncology Group 92–05 was an investigation of a weekendless version of CHART using 1.1 Gy given three times daily, 5 days per week over 5 weeks to a total dose of 79.2 Gy.[94] This trial has suffered from poor accrual. Preliminary results recently were reported for 35 patients: the median survival was 10.5 months and the 3-year survival was 18%, with an acute and late toxicity incidence of less than 10%.[95] A European randomized trial is underway to compare weekendless modifications of CHART with conventional RT.

Other Strategies

Split-course Radiotherapy. An alternative to a continuous schedule is two courses of radiation separated by a 2- to 3-week rest period. Split-course radiotherapy is tolerated more easily, especially when given concurrently with chemotherapy. Several randomized trials have failed to demonstrate any survival difference between split-course and continuous regimens.[57, 98, 121, 122] Nevertheless, split-course radiotherapy is not favored for curative regimens because significant repopulation of tumor cells can occur during the treatment break.

Radiation Sensitizers. One putative mechanism by which tumors fail to be cured by radiotherapy is the relative radioresistance of hypoxic cells in the center of a large tumor. Efforts to overcome this obstacle by the use of adjuncts such as hyperthermia, hypoxic cell sensitizing drugs, or hyperbaric oxygen have been disappointing. More encouraging results with cisplatin as a radiosensitizer paved the way to incorporating cytotoxic drugs as another means of enhancing radiation.[180] Other chemotherapeutic agents with radiosensitizing capability include carboplatin, vinorelbine, gemcitabine, irinotecan, and the taxanes.

Chemotherapy and Radiation Combinations

A significant advancement in the treatment of locally advanced NSCLC came with the addition of platinum-based chemotherapy to definitive RT. Cancer and Leukemia Group B (CALGB) 8433 was a seminal trial supporting the combined modality approach.[54] The trial compared induction chemotherapy followed by RT versus radiation alone. Chemotherapy consisted of two cycles of cisplatin and vinblastine. Radiotherapy was administered in standard 2-Gy fractions to a total dose of 60 Gy. The survival advantage for the chemoradiation arm was durable, although the number of long-term survivors in this study was small. At 7 years, more than twice as many patients were alive with chemoradiation than with radiation alone—13% versus 6%.[53]

A large intergroup trial[175, 177] and three subsequent meta-analyses, including one of 3033 patients in 22 randomized trials,[193] confirmed the superiority of combined modality treatment over radiation alone.[126, 152] Chemotherapy plus radiation is also superior to chemotherapy alone.[112] As a result, the American Society of Clinical Oncologists has recognized combined chemoradiation as the current standard of care for unresectable, nonmetastatic patients with NSCLC who fit the eligibility criteria of CALGB 8433.[8] This trial had been restricted to a selected group of functional patients with minimal weight loss. Radiation Therapy Oncology Group 97–10 is an ongoing study to confirm these findings in the poor-risk patient population.

The optimal sequencing of chemotherapy and RT remains controversial, although there is growing evidence to suggest that concurrent administration is better than sequential delivery. The West Japan Group conducted the first large-scale comparison of the two approaches.[71] The concurrent arm of 56-Gy split-course radiation with chemotherapy was compared with the sequential arm of the same chemotherapy followed by 56 Gy given continuously. The scheduled interruption of radiation was deemed necessary because of the high incidence of neutropenic fever in the dose-finding study. Overall response, median survival, and 5-year survival were all significantly better in the concurrent arm—85% versus 66%, 16.5 months versus 13.3 months, and 16% versus 9%, respectively. Early results from a cooperative group study (RTOG 94–10) also favor concurrent over sequential administration of chemoradiation.[46] In this study, 593 evaluable patients were randomized to induction cisplatin-vinblastine followed by standard RT, the same given concurrently, or cisplatin-etoposide plus concurrent hyperfractionated radiation. The median survival time for the combined concurrent group was 17 months, compared with 14.6 months ($P = .038$) for the sequential arm.

In contrast, a French phase III study did not find a statistically significant survival benefit for concurrent treatment. The trial randomized 212 patients to sequential cisplatin-vinorelbine and RT or concurrent cisplatin-etoposide and radiation followed by 2 cycles of cisplatin-vinorelbine.[80] Although local control was improved with concurrent administration, the median and 2-year survival were not prolonged. Ongoing studies to clarify this issue include the Locally Advanced Multimodality Protocol (LAMP trial), comparing induction chemotherapy followed by standard RT versus concurrent chemoradiation or induction chemotherapy followed by concurrent chemoradiation.[45]

The main concern with concomitant chemoradiotherapy is its toxicity. In the Japanese trial, as expected, concurrent therapy resulted in more hematologic toxicity. In the RTOG 94–10 trial, a dramatic increase in the incidence of severe nonhematologic toxicities was observed in the concurrent arms—48% versus 0%—mainly accounted for by acute esophagitis. A quality-adjusted time without symptoms or toxicity survival analysis that subtracts the time spent with toxicity from the overall survival time, however, demonstrated that survival benefit still outweighed the increase in toxicity. One strategy to overcome the problem of toxicity is to incorporate radiation protectors such as amifostine into the treatment program. In 25 patients receiving sequential cisplatin-vinblastine plus radiation, amifostine reduced cisplatin-related nephrotoxicity and radiation-induced esophagitis without compromising efficacy and survival.[195] Radiation Therapy Oncology Group 98–01 was opened to investigate further the role of amifostine in combined chemoradiotherapy.

Other possibilities being explored in the combined modality realm include the use of newer chemotherapeutic agents in combination with standard radiation,[31, 33, 158] hyperfractionated radiation,[32, 99–101, 109, 120] CHART,[10, 17, 192, 197] additional consolidative chemotherapy,[51, 74, 76, 116, 158] and induction chemotherapy plus concurrent chemoradiation.[45, 109, 110, 176, 205] Two consecutive studies by a Yugoslavian group compared weekly[99] or daily[100, 101] chemotherapy combined with hyperfractionated radiation to hyperfractionated radiation alone and demonstrated a superior survival for the combined treatment in both trials. Median survival times were 18 to 22 months, versus 8 to 14 months, and 3-year survival rates were 23% versus 7% to 11%. A phase II Southwestern Oncology Group study of concurrent chemoradiotherapy followed by three cycles of consolidation docetaxel resulted in a dramatic median survival time of 27 months, with 1-year survival of 76% and 3-year survival of 40%.[76] Table 2 summarizes the various approaches to combining chemotherapy and radiation.

STAGE IIIB AND IV DISEASE

Role of Palliative Radiotherapy

Advanced or metastatic NSCLC can produce a variety of debilitating and potentially life-threatening complications. Conventional schedules of radiation relieve symptoms of hemoptysis, chest pain, dyspnea, and cough in 50% to 80% of patients and hoarseness in a minority of cases.[15, 16, 114, 124, 187] Other indications include relief of superior vena cava syndrome, management of painful or potentially destabilizing bone metastases, and treatment of epidural or parenchymal brain lesions. Pleural effusions associated with NSCLC are unresponsive to RT, and thus patients with malignant effusions are treated with chemotherapy. Tube thoracostomy and chemical pleurodesis are indicated to alleviate the symptoms associated with large effusions.

Brain metastases are typically treated with whole-brain irradiation with only partial relief of symptoms for most patients.[19] In selected patients with solitary brain lesions, surgical excision plus radiation offers better local control and survival when compared with radiation only.[144] Stereotactic radiosurgery is becoming more widely available and may be more effective than whole-brain external-beam radiation. Currently, up to four lesions as large as 4 cm in diameter can be treated using single-fraction doses between 10 and 35 Gy.[6, 35, 58, 61, 131] In selected patients, this procedure is well tolerated and is successful in achieving local control in 70% to 95% of the patients. A multicenter retrospective comparison of stereotactic radiosurgery versus neurosurgical resection for selected patients who met the eligibility criteria used by Patchell et al[144] suggested that stereotactic radia-

Table 2. VARIOUS APPROACHES TO COMBINING CHEMOTHERAPY AND RADIATION

Chemoradiation Scheme	ORR (%)	MST (Months)	Survival (%)		Grade 3–4 Toxicity (%)		References
			1-Year	*2-Year*	*Esoph**	*Lung†*	
STD RT alone	43–55	9.6–11.4	40–47	13–21	N/R	N/R	53, 54, 177 117, 119
C → STD RT	47–56	12–13.7	50–59	21–32	N/R	N/R	53, 54, 177 117, 119
C/STD RT	67–86	13–20.5	56–61	33–38	37–46	0–12	180, 31, 33
C/HFX RT	74–94	14.3–25	58–83	35–51	15–53	12–25	99, 100, 120, 109, 32 10, 197, 17
C/HART	41	9–11.6	N/R	N/R	39	8	205, 109
C → C/RT	77–88	15.5–20	65–73	34–35	9–15	4–26	76, 116, 158
C/RT → C	71–77	14.5–27	58–76	40–54	10–38	0–3	

STD RT = Standard radiotherapy; → = sequential; / = concurrent; C = chemotherapy; HFX RT = hyperfractionated radiotherapy; HART = hyperfractionated accelerated radiotherapy; ORR = overall response rate; MST = median survival time; N/R = not reported.
*Esophagitis: grade 3 = dysphagia requiring intravenous hydration, grade 4 = complete obstruction requiring parenteral nutritional support.
†Pulmonary fibrosis: grade 3 = radiographic changes and requiring oxygen, grade 4 = radiographic changes and requiring assisted ventilation.

tion was equivalent to surgery.[9] To date, no prospective data are available.

Large-dose or hypofractionated schedules of radiation to chest lesions have been evaluated to conserve resources and increase convenience for patients. The Medical Research Council has conducted two randomized trials demonstrating that two weekly fractions of 8.5 Gy were equivalent to a single fraction of 10 Gy[15] or standard 30 Gy in 10 fractions.[16] The median survival of the patients included in these studies was approximately 4 to 6 months. The single-fraction approach, however, is not practiced commonly in the United States.

Role of Chemotherapy

With supportive care measures only, the median survival of patients with metastatic NSCLC is 16 to 17 weeks, and 1-year survival is 10% to 15%.[193] Ten randomized trials[26, 27, 37, 44, 75, 85, 104, 153, 157, 206] that have been evaluated further by four independent meta-analyses[89, 125, 190, 193] showed that combination chemotherapy and platinum-based chemotherapy in particular resulted in improved median survival of 25 weeks and a gain in 1-year survival of about 10%. The studies included in the meta-analyses utilized regimens that included cisplatin, ifosfamide, etoposide, vindesine, and mitomycin C, the single-agent response rates of which range from 10% to 25%.[189] Of these, cisplatin and cisplatin-based regimens continue to be the mainstay of first-line treatment.

Since 1990, five new agents were identified as having promising activity against NSCLC, as summarized in Table 3. As single agents, these drugs had higher overall response rates and were generally better tolerated than cisplatin. Numerous platinum- and nonplatinum-based two-drug combinations incorporating these newer agents were developed for the treatment of advanced NSCLC (Table 4). Randomized trials have demonstrated that several of these doublets are superior to cisplatin alone or the older cisplatin-etoposide or cisplatin-vindesine regimens, with improved 1-year and 2-year survival rates of 30% to 40% and 15%, respectively.[161, 179, 181, 201] No single combination has emerged as the superior regimen.

With the benefit of modern chemotherapy established for younger, highly functional patients, a recent direction in research has been to evaluate its use in the elderly or unfavorable patient populations. Several phase II trials of vinorelbine[21, 36, 67, 199, 202] and gemcitabine[86, 159, 184] as single agents or in combination,[14, 67, 86] specifically in the elderly population, have demonstrated good tolerability and modest antitumor activity. A recent multicenter randomized trial Elderly Lung Cancer Vinorelbine Italian Study (ELVIS) of vinorelbine versus best supportive care showed a significant survival advantage for the vinorelbine arm.[85] An interim analysis of a trial comparing gemcitabine and vinorelbine polychemotherapy versus single-agent vinorelbine showed that 1-year survival was superior with combination chemotherapy—30% versus 13%.[67] Another study comparing gemcitabine and vinorelbine combination to vinorelbine or gemcitabine alone, however, found no difference between combination and single-agent chemotherapy.[87]

Patients failing first-line chemotherapy are becoming candidates for salvage therapy in increasing numbers because of the availability of drugs that retain some degree of activity and have acceptable toxicity. Docetaxel has undergone the most extensive testing in this setting and is the

Table 3. SINGLE AGENT ACTIVITY IN NON–SMALL CELL CANCER

Agent	Mechanism of Action	Evaluable Patients	ORR (%)	References
OLDER AGENTS				
Cisplatin	Inhibition of DNA synthesis by cross-links	568	21	23
Carboplatin	Inhibition of DNA synthesis by cross-links	491	10	22
Etoposide	Topoisomerase II poison	128	8	143
NEWER AGENTS				
Vinorelbine	Inhibition of tubulin assembly	840	8–37	25, 42, 49, 50, 73, 88, 118, 130, 202, 204
Paclitaxel	Inhibition of tubulin disassembly	454	10–36	4, 5, 29, 72, 77, 91, 136, 139, 155, 156, 198
Docetaxel	Inhibition of tubulin disassembly	553	19–38	28, 63, 66, 81, 113, 115, 132, 135, 150, 168, 208
Gemcitabine	Inhibition of DNA synthesis	651	18–26	1, 7, 64, 70, 78, 92, 123, 149, 159, 194, 210
Irinotecan	Topoisomerase I poison	127	12–32	69, 141, 142

ORR = Overall response rate.

only agent approved in the United States for the treatment of refractory NSCLC. When compared with best supportive care in platinum-resistant patients, docetaxel resulted in an overall response rate of 7%, a longer time to progression of 10.6 versus 6.7 weeks, and an increased median survival time of 7 versus 4.6 months.[185] Quality of life also was improved. A second phase III trial compared docetaxel with vinorelbine or ifosfamide and found docetaxel to be superior in terms of overall response, time to progression, and 1-year survival.[62] Randomized trials in the elderly and refractory populations are summarized in Table 5.

Role of Molecular Targeted Therapy

Several novel molecular targets governing the cell cycle, growth-signaling pathways, and angiogenesis have been identified as being abnormal, and therefore exploitable, in NSCLC. Figure 1 provides a schematic overview of these targets and their modulators. Tumor angiogenesis (Fig. 1*A*) is a multistep process involving proliferation of endothelium, breakdown of the basement membrane, and migration of endothelial cells. Vascular endothelial growth factor (VEGF), often overexpressed in cancers, is the most potent mitogen implicated

Table 4. PLATINUM-BASED CHEMOTHERAPY DOUBLETS IN NON–SMALL CELL LUNG CANCER

Regimen	Patients	ORR (%)	Survival		Comments
			MST (Months)	*1-Year (%)*	
Cisplatin-etoposide	1573	12–34	5.1–7.6	32*	Equivalent to GEM but more toxic[123] Equivalent to CPPD-GEM[24] Inferior to CPPD-PAC[18]
Cisplatin-vindesine	980	19–43	5.8–11	27†	Superior to BSC[157, 206] Inferior to CPPD-VNB[118]
Cisplatin-vinorelbine	1025	26–57	7.7–11	28–36	Superior to CPPD-VDS[118] Superior to VNB alone[118] Superior to CPPD alone[207] Equivalent to CARB-PAC[106]
Cisplatin-paclitaxel	968	25–55	8.1–10	35–43	Superior to CPPD-ETOP[18] Equivalent to CPPD alone[79]
Carboplatin-paclitaxel	822	25–62	6.5–12.8	31–55	Equivalent to CPPD-VNB[106]
Cisplatin-docetaxel	304	21–48	8.4–13	33–48	MTD: CPPD-100/DOC-75 or CPPD-25/DOC-100
Cisplatin-gemcitabine	724	30–65	8.6–14.2	32–61	Superior to CPPD alone[170] Equivalent to CPPD-ETOP[24] Equivalent to MIC[43]
Cisplatin-irinotecan	305	29–52	9.9–11.6	33–40	Superior to CPPD-VDS[68]

ORR = Overall response rate; MST = median survival time; CPPD = cisplatin; ETOP = etoposide; VDS = vindesine; VNB = vinorelbine; PAC = paclitaxel; CARB = carboplatin; DOC = docetaxel; GEM = gemcitabine; CPT = irinotecan; BSC = best supportive care; MIC = mitomycin, ifosfamide, cisplatin; MTD = maximum tolerated dose.

*Available from two studies only.

†Reported in one study only.

Table 5. RANDOMIZED TRIALS OF CHEMOTHERAPY IN SPECIAL POPULATIONS

Reference	Regimen	Patients			ORR (%)	Survival		*P*-Value
		N	*Age*	*PS 2 (%)*		*MST (Months)*	*1-Year (%)*	
Elderly/Poor Performance Status								
ELVIS trial[85]	VNB	74	70–85	24	20	6.5	32	.03
	BSC	75	70–86	24	—	4.9	14	
MILES trial[86]	GEM	49	70–82	16	18			
	GEM + VNB VNB-ongoing	49	70–82	14	18	32[a]	33[a]	—
Frasci et al[67]	VNB	60	71–81	22	15	4.2	13	
	GEM + VNB	60	71–83	27	22	6.8	30	<.01
Refractory to First-Line Chemotherapy								
Shepherd et al[185]	DOC	84	37–76	24	7	7.0	37	.003
	BSC	100	28–77	25	—	4.6	11	
Fossella et al[62]	DOC100	126	60[b]	17	11	5.5	21	N/S
	DOC75	125	59[b]	18	7	5.7	32	.025
	VNB or IFOS	123	60[b]	15	1	5.6	19	

PS 2 = performance status of 2 (ECOG scale); ORR = Overall response rate; MST = median survival time; ELVIS = elderly lung cancer vinorelbine italian study; MILES = multicenter italian lung cancer in the elderly study; GEM = gemcitabine; VNB = vinorelbine; DOC = docetaxel; BSC = best supportive care; IFOS = ifosfamide; N/S = not statistically significant.

[a]GEM and GEM + VNB combined.

[b]media age.

in endothelial proliferation. This step can be inhibited by neutralizing antibodies to VEGF[102] or VEGF receptors. In a randomized phase II study comparing two doses of anti-VEGF antibody (Rhumab) plus chemotherapy versus chemotherapy alone in NSCLC, the best response rate and survival were seen with the high-dose Rhumab-chemotherapy combination.[52]

Angiogenesis is facilitated by matrix metalloproteinases (MMPs), enzymes capable of digesting the extracellular proteins and the basement membrane. Solid tumors can synthesize and activate MMPs, notably MMP-2 and MMP-9. Several inhibitors of MMPs have entered clinical trials, but results so far have been disappointing.[165, 188] Since then, at least 18 different MMPs have been identified. It is possible that inhibitors tested to date have not had appropriate specificity. Newer MMP inhibitors continue to be tested in clinical trials.[96, 168]

Recent data suggest that cyclooxygenase-2 (COX-2), critical for the conversion of arachidonic acid to prostaglandins, contributes to tumorigenesis and new vessel formation. Cyclooxygenase-2 is overexpressed in a wide variety of premalignant and malignant conditions, including NSCLC, and results in increased expression of MMPs and endothelial growth factors such as VEGF.[48] In experimental animals, selective inhibitors of COX-2 prevent new tumor formation, slow the growth of established tumors, and decrease the number and size of metastases.[129] COX-2 inhibitors also may enhance the antitumor effects of chemotherapy[138] and radiation.[134] Clinical testing of COX-2 inhibitors is underway.

Epidermal growth factor receptor (EGFR) is a tyrosine kinase-bearing transmembrane receptor found on most NSCLC cells (Fig. 1*B*). When bound by a growth factor, tyrosine residues located on the internal domain of the receptor are autophosphorylated and trigger a cascade of downstream effector molecules, leading to proliferation. Epidermal growth factor receptor is overexpressed in NSCLC and confers a poor prognosis. C225 is a humanized monoclonal antibody that binds EGFR with high affinity and inhibits the growth of EGFR-expressing cancer cells in vitro. C225 has been shown to be synergistic with various chemotherapy drugs and radiation in NSCLC xenograft models.[154] More than 500 patients have been treated with C225 with encouraging results in advanced head and neck, colon, and pancreatic cancers, especially when C225 was combined with radiation[160] or cisplatin,[13] irinotecan, and gemcitabine, respectively.[133] Specific trials in NSCLC have not yet been completed.

ZD 1839 (Iressa) is a potent, selective inhibitor of EGFR-associated tyrosine kinase.[11] In dose-finding studies, antitumor activity was most evident for NSCLC. Measurable responses lasting 3 to more than 9 months were observed in 8 of 77 patients with refractory NSCLC.[12, 60, 140] Iressa currently is undergoing further testing alone or in combination with chemotherapy in the treatment of advanced NSCLC. Other EGFR-tyrosine kinase inhibitors under clinical investigation include OSI-774[148, 164] and PKI166.

Akt or protein kinase B (PKB) is an important effector molecule in the EGFR-mediated growth signaling pathway.[34] Autophosphorylated tyrosine residues on EGFR recruit phosphatidylinositol 3-kinase to the membrane where it phosphorylates PIP_2 to PIP_3. PIP_3, in turn, recruits PIP_3-dependent

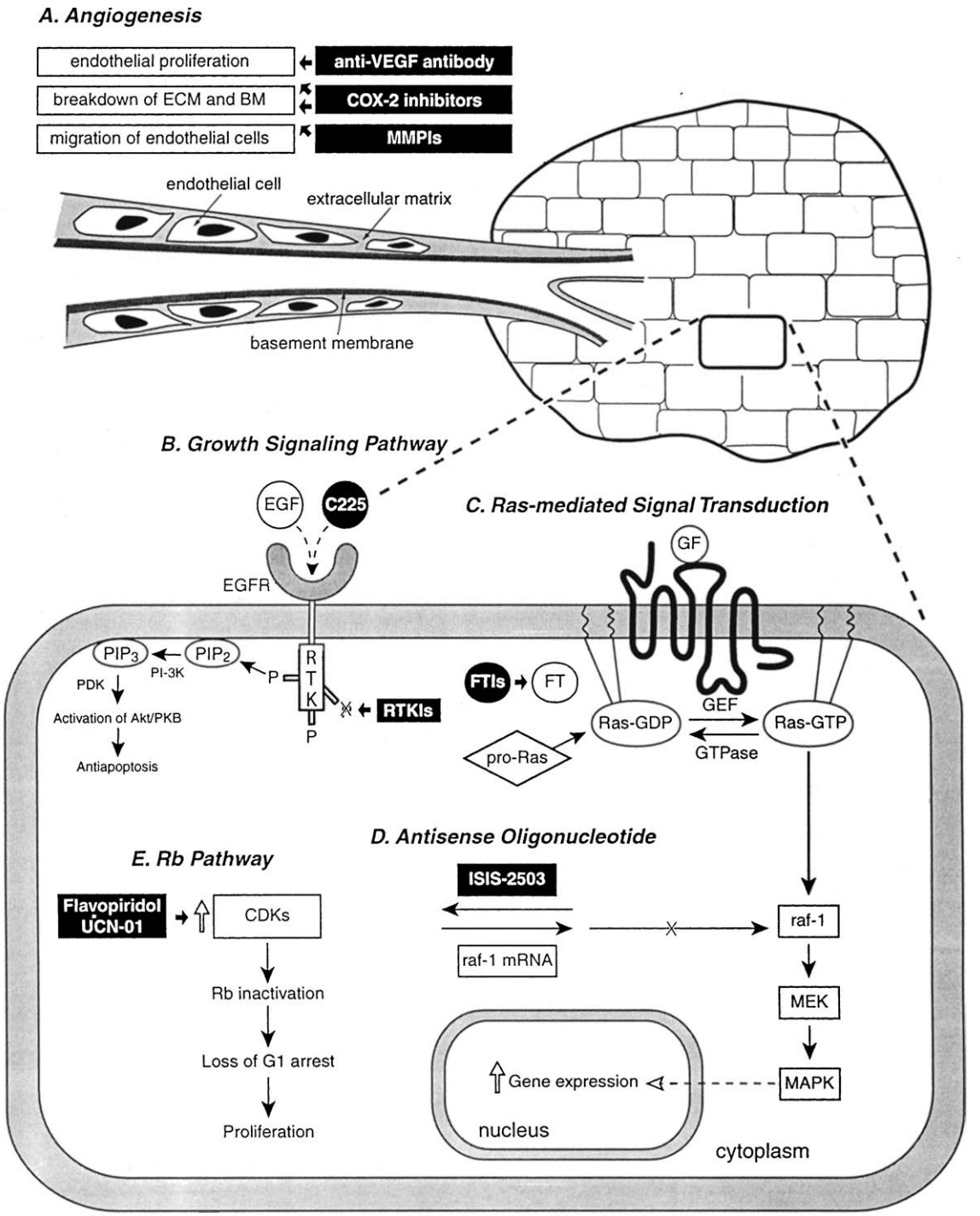

Figure 1. *See legend on opposite page*

kinase (PDK) and protein kinase B. Protein kinase B is phosphorylated by PIP_3-dependent kinase and is released from the membrane to the cytoplasm and the nucleus. Activation of PKB results in increased protein synthesis and antiapoptosis. Alternatively, PKB is activated by insulin and plays a role in glucose metabolism. Constitutive activity of PKB was found in 16 of 17 NSCLC cell lines and conferred enhanced cancer cell survival and resistance to chemotherapy and radiation.[20] Inhibition of PKB is being developed clinically.

The *ras* protein is a key intermediate in the signal transduction pathways. Membrane-associated *ras* is able to relay a variety of signals from membrane receptors down to the cytoplasm through a series of protein kinases, governing processes such as growth, differentiation, and apoptosis. Its association with the membrane depends on the addition of a farnesyl group to the inactive proprotein by farnesyltransferase. Interference of farnesylation prevents *ras* from becoming biologically active, and farnesyltransferase inhibitors (FTIs) therefore are being developed as potential anticancer therapy (Fig. 1*C*).[166] R115777 was the first of the FTIs to enter clinical trials[211] and several phase I studies of R115777 in combination with chemotherapy were reported in 2001, showing relevant antitumor activity.[2, 97, 151, 203] SCH66336 given alone did not result in partial or complete responses[59] but, when combined with paclitaxel, resulted in major responses in 8 of 21 patients with NSCLC, head and neck cancers, or salivary gland tumors.[107]

Ras activation leads to the activation of *raf-1*, a protein kinase downstream from *ras*. Activated *raf-1* phosphorylates the MAP kinase kinase, which, in turn phosphorylates the mitogen-activated protein kinase. Mitogen-activated protein kinase translocates to the nucleus and ultimately increases gene expression and proliferation.[166] Inhibition of *raf-1* results in growth inhibition. One strategy developed to disrupt the *raf-1* pathway is antisense therapy. Antisense oligonucleotides bind mRNAs in the sense orientation and prevent the expression of the protein product (Fig. 1*D*). ISIS 2503 is a *raf-1* antisense oligonucleotide that has completed phase II testing in advanced NSCLC, with 7 of 20 patients achieving disease stabilization.[47] An antisense inhibitor of protein kinase C-α—ISIS 352—with carboplatin and paclitaxel also has completed phase II testing in NSCLC, with 42% major responses seen among 48 patients and median survival of 19 months and 1-year survival, 75%.[209]

Retinoblastoma (Rb) is a tumor-suppressor gene responsible for regulating G1 to S phase transition. Phosphorylation by cyclin-dependent kinases (CDKs) results in Rb inactivation, leading to loss of G1 arrest and uncontrolled proliferation. Most cancers exhibit abnormalities in the Rb pathway by several different mechanisms, including overexpression of cyclins or CDKs, underproduction of cyclin or CDK inhibitors, or Rb mutations. Cyclin-dependent kinases have been a target of several novel compounds aimed at inhibiting Rb phosphorylation (Fig. 1*E*). Flavopiridol is a potent, nonselective inhibitor of CDK that has completed phase II testing.[182, 191] UCN-01 is a relatively specific inhibitor of CDK2 with the ability to induce G1 arrest in Rb-expressing cells. It may lack activity in Rb-negative cancers such as small cell lung cancer (SCLC), however.[178, 183]

Several new agents directed against an established target, the mitotic spindle, are under development. Epothilone B, a macrolide with the ability to induce hyperstable tubulin polymers, was

Figure 1. Molecular targets and their modulators in non–small cell lung cancer (NSCLC). *A*, Anti-VEGF antibody neutralizes vascular endothelial growth factor (VEGF) and blocks endothelial proliferation; inhibitors of matrix metalloproteinases (MMPs) block the enzymatic digestion of the extracellular matrix (ECM) and the basement membrane (BM); COX-2 is overexpressed in NSCLC and results in increased expression of MMPs and VEGF, and antiangiogenic effects of COX-2 inhibitors have been demonstrated in animals. *B*, C225, a humanized monoclonal antibody against epidermal growth factor receptor (EGFR), competes with natural ligands such as epidermal growth factor (EGF) and causes down-regulation of EGFR leading to growth inhibition; inhibitors of EGFR-associated tyrosine kinase (RTK) interfere with growth signaling; autophosphorylated tyrosine residues on EGFR recruit phosphatidylinositol 3-kinase (PI-3K) to the membrane where it phosphorylates PIP_2 to PIP_3, which in turn recruits PIP_3-dependent kinase (PDK) and Akt/protein kinase B (PKB). Activation of PKB by PDK results in antiapoptosis. *C*, Farnesyltransferase (FT) transforms an inactive *Ras* proprotein into an active, membrane-associated form, ready to relay a variety of signals from membrane receptors down to the cytoplasm, governing such processes as growth and differentiation; farnesyltransferase inhibitors (FTIs) prevent *Ras* from becoming biologically active, thereby blocking *Ras*-mediated signal transduction pathways. *D*, *Raf-1* is an important effector of *Ras* function. Once activated by *Ras*, *raf-1* activates MAP kinase kinases (MEKs), which in turn activate the mitogen-activated protein kinases (MAPKs); MAPKs translocate to the nucleus, ultimately leading to increased gene expression and proliferation. ISIS 2503 is an antisense oligonucleotide that depletes *raf-1* mRNAs by binding in the sense orientation and thus inhibiting the expression of *raf-1* protein product. *E*, Cyclin dependent kinases (CDKs) are overexpressed in NSCLC. Phosphorylation by CDKs results in retinoblastoma (Rb) inactivation, leading to loss of G1 arrest and uncontrolled proliferation. CDK inhibitors, such as flavopiridol and UCN-01, prevent Rb phosphorylation and inactivation, thereby restoring G1 arrest.

shown to be more potent than paclitaxel and to be active in human cancer cell lines resistant to paclitaxel because of multidrug resistance or β-tubulin mutations.[111] A phase I study of epothilone B was reported in 2001, confirming activity in advanced malignancies.[167] Several new taxane analogues are in development and are showing activity against lung cancer.[3]

SUMMARY

The treatment options for unresectable stage III NSCLC include definitive RT, chemotherapy, combined chemoradiotherapy, or supportive care. Compared with radiation alone or chemotherapy alone, the combination of chemotherapy and standard RT confers a modest survival benefit at the cost of increased toxicity for patients with an excellent performance status. For metastatic disease, combination chemotherapy—in particular, platinum-based regimens—improves symptom control and survival. Newer chemotherapeutic agents with higher response rates and favorable toxicity profiles are improving outcome even for the elderly and debilitated patients and those refractory to first-line chemotherapy. Evolving understanding of the molecular events in tumorigenesis is uncovering a host of promising targets for mechanism-based therapy. Many of these novel target modulators likely will require combination with conventional chemotherapy for optimal results.

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