Treatment of Non-small Cell Lung Cancer, Stage IV*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Background: **Stage IV non-small cell lung cancer (NSCLC) remains a treatable but incurable disease.**

Methods: **A MEDLINE search was performed to identify pertinent peer-reviewed articles that addressed the questions posed for this section. The writing committee developed and graded recommendations, which were subsequently approved by the American College of Chest Physicians.**

Results: **Platinum-based doublets remain the standard of care in patients with good performance status (PS); there is no evidence that the addition of a third cytotoxic agent improves survival. Likewise, with only one exception, the addition of a new targeted or biological agent to platinum-based doublets does not improve survival. The one exception is the addition of bevacizumab, an antiangiogenic agent, to carboplatin/paclitaxel in patients with stage IV disease and good PS. Patients for whom bevacizumab is recommended must also be selected on the basis of histology (nonsquamous), absence of brain metastases and hemoptysis, and no indication for therapeutic anticoagulation. In patients with stage IV NSCLC and PS of 2, chemotherapy is recommended, but the optimal approach has not been defined. Elderly patients, defined as ≥ 70 years old, also derive benefit from chemotherapy. Most elderly patients should receive single-agent chemotherapy, but elderly patients with good PS and without significant comorbidities seem to derive a similar benefit from platinum-based doublets compared with their younger counterparts without a prohibitive difference in treatment toxicities. Because stage IV NSCLC is incurable, quality-of-life issues are important, and tools exist to monitor a patient's quality of life during therapy. Last, patients need to be informed of the implication of the diagnosis of stage IV NSCLC and be educated about treatment options that are available to them.**

Conclusions: **Advances have been made in stage IV NSCLC, and the appropriate use of chemotherapy continues to evolve on the basis of well-designed clinical trials that address critical issues in this population.** ***(CHEST 2007; 132:277S–289S)***

Key words: chemotherapy; non-small cell lung cancer; quality of life; targeted therapy

Abbreviations: ACCP = American College of Chest Physicians; BSC = best supportive care; CALGB = Cancer and Leukemia Group B; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C3 = European Organization for Research and Cancer Treatment Quality of Life Questionnaire; FACT-L = Functional Assessment of Cancer Therapy-Lung; FLIC = Functional Living Index-Cancer; HRQOL = health-related quality of life; NSCLC = non-small cell lung cancer; PS = performance status; QOL = quality of life

Lung cancer remains the leading cause of cancer-related mortality in the United States. In 2006, there will be approximately 170,000 new cases of lung cancer diagnosed and roughly 158,000 deaths from lung cancer.[1] The majority (85%) of patients who receive a diagnosis of lung cancer will have non-small cell lung cancer (NSCLC).[2] It is estimated that 40% of patients with newly diagnosed NSCLC will have stage IV disease. In 2003, the American College of Chest Physicians (ACCP) issued its first guidelines that

included recommendations for chemotherapeutic management of stage IV NSCLC.[3] Table 1 summarizes the recommendations endorsed by the ACCP in 2003. In brief, these recommendations supported the use of chemotherapy on the basis of the performance status (PS) of the patient; in patients with stage IV NSCLC and good PS, chemotherapy clearly improves survival and palliates disease-related symptoms. The role of chemotherapy in patients with poor PS was less certain. Second-line chemotherapy also had a survival and palliative effect in patients with good PS. The duration of first-line chemotherapy should be brief (three to four cycles), and there was no clearly superior regimen in the first-line setting. Patient preferences should be respected, and educating patients about the advantages and disadvantages of chemotherapy was advocated.

The purpose of the stage IV guideline update is to address additional questions raised by the ACCP having pertinence to the everyday management and evaluation of advanced stage IV NSCLC. Although this chapter concerns stage IV, the recommendations also apply to certain subsets of patients with stage IIIB, as did the 2003 recommendations. The subsets of patients who have stage IIIB and are treated as though they have stage IV disease include patients with malignant pleural or pericardial effusions, with advanced ipsilateral supraclavicular adenopathy, and whose intrathoracic disease is not amenable to combined modality approaches.

Materials and Methods

In light of the recommendations made in 2003, additional questions that were believed to be pertinent to patients with advanced stage IIIB/IV NSCLC were asked. A systematic review of the literature was undertaken by the multidisciplinary writing committee to identify published materials, including both original articles and guidelines, that address lung cancer diagnosis, management, and treatment. Materials that are appropriate to this topic were obtained by literature search of a computerized database (MEDLINE) to identify relevant articles for review. Recommendations were developed by the writing committee and graded by a standardized method (see "Methodology for Lung Cancer Evidence Review and Guidelines Development" chapter). These recommendations were then approved by the Thoracic Oncology NetWork, Health and Science Policy Committee, and the Board of Regents of the ACCP.

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Results

Is There an Advantage to Using Three Chemotherapeutic Agents Compared With Two in Patients With Stage IV NSCLC and Good PS?

The 2003 ACCP recommendations defined platinum-based doublets as the standard of care for patients with stage IV NSCLC and good PS.[3] Delbaldo et al[4] reported a metaanalysis that included 13,601 patients in 65 trials and showed that two chemotherapeutic agents led to superior response and survival rates in patients with stage IV NSCLC compared with single agents (Table 2). Since the report of that metaanalysis, platinum-based doublets were shown to be superior to single-agent therapy in three randomized trials.[5–7] Although overall survival was statistically superior in only one of the three trials, the overall therapeutic efficacy, including response rate and progression-free survival, improved with the doublets with no significant cost in toxicity or quality of life (QOL).

Several large, randomized trials[3] have compared various platinum doublets (both cisplatin based and carboplatin based) and failed to identify a superior regimen. The only potential exception was the TAX 326 trial,[8] which demonstrated improved QOL and a trend toward improved survival (statistically, it was "noninferior") for cisplatin-docetaxel compared with cisplatin-vinorelbine. This experience, although valid, remains an exception, and cisplatin-docetaxel has not been widely adopted as the "preferred regimen." There is general agreement that either cisplatin or carboplatin combined with a taxane (paclitaxel or docetaxel), gemcitabine, vinorelbine, or irinotecan can be used in the first-line treatment of patients with advanced NSCLC and good PS.

A number of randomized trials[4] have tested the addition of a third chemotherapeutic agent to existing doublets. As shown in Tables 2, 3, these "triplets" consistently failed to show superiority over established two-drug combinations with regard to survival, although response rates were improved. In most trials, these efficacy parameters were at best comparable, whereas toxicity was substantially more pronounced with the triplets. Only one trial[9] showed better results for a triplet compared with a doublet, but the result seen in this trial stands alone and has not been reproduced by other investigators.[10]

Table 1—*Summary of 2003 Recommendations in Treatment of Stage IV NSCLC

Level of Evidence	Benefit	Grade	Recommendation
PS 0–1, good	Substantial	A	†
PS 2, poor	Small/weak	B	†
PS 3–4, fair	Moderate	B	†
Good	Substantial	A	Platinum-based therapy improves survival over BSC in patients with good PS (0–1).
Poor	Small/weak	I	New single agents alone are equivalent to platinum-based combinations.
Fair	Moderate	B	Combination regimens that incorporate the new single agents with a platinum should be used.
Good	Substantial	A	There is not one clearly superior platinum-based combination regimen.
Good	Substantial	A	Duration of first-line therapy should be 3–4 cycles.
Good	Moderate	B	Second-line treatment should be offered to patients with a good PS at the time of disease progression.
Good	Moderate	B	Chemotherapy has a palliative effect on disease-related symptoms and can improve QOL.
Fair	Moderate	B	Patient preferences need to be considered and respected with regard to the decision to treat with chemotherapy.
Poor	Substantial	C	Patients with stage IV NSCLC should be referred to a physician with specialized training in oncology.
Good	Substantial	A	Combination platinum-based chemotherapy can be administered safely with acceptable and manageable toxicity.

*From Socinski et al.[3]
†PS should be used to select patients for therapy because it is a consistent prognostic factor for survival.

The advent of molecular-targeted agents has raised expectations that these agents, which are different from traditional chemotherapeutic drugs, could be added to standard doublets with enhanced efficacy and no additional toxicity. Large, randomized trials tested the two available tyrosine kinase inhibitors, gefitinib and erlotinib, in combination with cisplatin-gemcitabine[11] and carboplatin-paclitaxel.[12,13] Unfortunately, no significant difference in survival was observed with the addition of the two novel agents when used concomitant with chemotherapy in any of the four trials, which together accrued nearly 4,000 patients worldwide. However, in a subset analysis of one of the trials,[12] patients with no history of smoking experienced a significant benefit when treated with erlotinib plus chemotherapy compared with chemotherapy alone. This observation is being tested in a prospective manner. Other promising agents, including but not limited to metalloproteinase inhibitors (prinomastat), antisense therapy (ISIS 3521), farnesyl transferase inhibitors (lonafarnib), and retinoid derivatives (bexarotene), all failed to improve outcomes when added to standard chemotherapy in patients with advanced NSCLC.

Bevacizumab, an anti-vascular endothelial growth factor humanized monoclonal antibody, already approved for the treatment of advanced colorectal cancer, was evaluated in a large, randomized, phase III trial conducted by the Eastern Cooperative Oncology Group (ECOG) and referred to as ECOG 4599.[14] This trial randomly assigned patients with advanced NSCLC, except squamous histology, to carboplatin-paclitaxel with or without bevacizumab. Other exclusion criteria were history of hemoptysis, history of brain metastases, history of bleeding or thrombotic disorders, or need for full anticoagulation. The primary reason for the more selected patient population was the risk for hemoptysis, sometimes fatal, observed in the initial phase II trial of chemotherapy plus bevacizumab.[15]

The ECOG 4599 trial enrolled 855 eligible patients with PS of 0 to 1. All efficacy end points, including response rate and progression-free and overall survival, were significantly better in the bevacizumab arm. Among 420 patients who were treated with bevacizumab, toxicity was in general tolerable, except for five deaths secondary to hemoptysis. This trial is

Table 2—*Metaanalysis Addressing the Number of Cytotoxic Agents in Advanced NSCLC

	Ratio (95% CI)		
Regimen	Response Rate†	Median Survival	1-yr Survival‡
Two agents vs one agent	0.42 (0.37–0.47)	0.83 (0.79–0.89)	0.80 (0.70–0.91)
Three agents vs two agents	0.66 (0.58–0.75)	1.00 (0.94–1.06)	1.01 (0.85–1.21)

*From Delbaldo et al.[4] CI = confidence interval.
†Absolute benefit: 13% for two-agent vs one-agent regimens; 8% for three-agent vs two-agent regimens.
‡Although there was a 5% absolute benefit for two-agent vs one-agent regimens, there was no benefit for three-agent vs two-agent regimens.

Table 3—*Randomized Trials Evaluating Three-Drug vs Two-Drug Combinations in Advanced NSCLC

Study	Patients Analyzed/Randomly Assigned, No.	Treatment Regimen		Response Rate		1-yr Survival	
		Doublet	Triplet	Ratio (95% CI)	p Value	Ratio (95% CI)	p Value
Sandler et al[14]/ 2006	878/878	Paclitaxel plus carboplatin	Paclitaxel plus carboplatin plus bevacizumab	0.32 (0.22–0.47)	< 0.0001	0.77 (0.65–0.93)	0.07
Bissett et al[74]/ 2005	333/362	Cisplatin plus gemcitabine	Cisplatin plus gemcitabine plus prinomastat	0.95 (0.58–1.5)	0.81	0.92 (NR)	0.45
Douillard et al[75]/ 2004	75/75	Paclitaxel plus carboplatin	Paclitaxel plus carboplatin plus BMS-275291	2.0 (0.69–5.7)	NR		
Gatzemeier et al[76]/ 2004	101/103	Cisplatin plus gemcitabine	Cisplatin plus gemcitabine plus trastuzumab	1.24 (0.56–1.40)	NR		
Giaccone et al[11]/ 2004	1,093/1,093	Cisplatin plus gemcitabine	Cisplatin plus gemcitabine plus gefitinib	0.87 (0.67–1.13)	NS	0.97 (NR)	0.456
Herbst et al[13]/ 2004	1,037/1,037	Paclitaxel plus carboplatin	Paclitaxel plus carboplatin plus gefitinib	0.91 (0.69–1.2)	NR	0.93 (NR)	NS
Herbst et al[12]/ 2005	1,059/1,078	Paclitaxel plus carboplatin	Paclitaxel plus carboplatin plus erlotinib	0.87 (0.65–1.2)	0.36	NR	NR
Johnson et al[15]/ 2004 (NR)	99/99	Paclitaxel plus carboplatin	Paclitaxel plus carboplatin plus bevacizumab	0.56 (0.22–1.4)	"trend"		
Leighl et al[77]/ 2005	774/774	Paclitaxel plus carboplatin	Paclitaxel plus carboplatin plus BMS-275291	1.45 (1.1–2.0)	0.10		
Danson et al[78]/ 2003	361/372	Gemcitabine plus carboplatin	MIC/MVC	0.91 (0.59–1.4)	NR	0.97 (NR)	NR
Gebbia et al[79]/ 2002	247/247	Cisplatin plus vinorelbine	Cisplatin plus vindesine plus mitomycin C	0.91 (0.55–1.5)	0.13	0.97 (NR)	NS
Rudd et al[80]/ 2005	422/422	Gemcitabine plus carboplatin	MIC	1.03 (0.64–1.7)	0.84	1.17 (1.05–1.3)	NR

*NR = not reported; NS = not significant; MIC = mitomycin, ifosfamide, cisplatin; MVC = mitomycin, vinblastine, cisplatin; BMS = Bristol Myers Squibb. See Table 2 for expansion of abbreviation.

the first to demonstrate a superiority for a triplet over a doublet, with the understanding that bevacizumab is not a conventional chemotherapeutic agent. It is also the first trial to show a survival benefit for the use of an angioinhibiting agent in the treatment of advanced NSCLC.

Recommendations

1. In patients with stage IV NSCLC and good PS, two-drug combination chemotherapy is recommended. The addition of a third cytotoxic chemotherapeutic agent is not recommended because it provides no survival benefit and may be harmful. Grade of recommendation, 1A

2. Bevacizumab improves survival combined with carboplatin and paclitaxel in a clinically selected subset of patients with stage IV NSCLC and good PS (nonsquamous histology, lack of brain metastases, and no hemoptysis). In these patients, addition of bevacizumab to carboplatin and paclitaxel should be considered a therapeutic option. Grade of recommendation, 1A

Should Elderly Patients Be Treated Differently From Younger Patients?

Approximately two thirds of patients with NSCLC are ≥ 65 years old, and approximately 40% are ≥ 70 years old.[16] Surveillance, Epidemiology, and End Results data[17] suggest that the percentage of patients who are > 70 years old is closer to 50%, yet elderly patients are generally underrepresented on clinical trials; participation of elderly patients with advanced disease in national clinical trials has ranged from 15% in the early 1990s to 29% in more recent studies.[18] Although the trend in enrollment is en-

couraging, it demonstrates a residual bias against treating elderly patients with advanced NSCLC. Indeed, Ramsey et al[17] reviewed the Surveillance, Epidemiology, and End Results Medicare data from 1994 to 1999 and found a much lower rate of chemotherapy use than expected for the overall population. It also suggests that the elderly may have more comorbidities or a higher rate of functional compromise that would make study participation difficult, if not contraindicated. There is general agreement that the elderly fall into two categories: the "fit" and the "unfit." Having said this, there is not general agreement as to how to define these two groups accurately or how the increasing incidence of comorbidities in elderly patients influences treatment choices or recommendations.

The notion that chemotherapy was too toxic or provided only marginal benefit for elderly patients was first challenged by the Elderly Lung Cancer Vinorelbine Italian Study[19] (Table 4). The study randomly assigned 154 patients who were > 70 years old to vinorelbine vs supportive care. Patients who were treated with vinorelbine had a 1-year survival rate of 32%, compared with 14% for those who were treated with supportive care alone. QOL parameters were also significantly improved in the chemotherapy arm, and toxicity was acceptable. A more recent trial[20] from Japan compared single-agent docetaxel with vinorelbine in 180 elderly patients with good PS. Response rates and progression-free survival were significantly better with docetaxel (22% vs 10%; 5.4 months vs 3.1 months, respectively), whereas median and 1-year survival rates did not reach statistical significance (14.3 months vs 9.9 months; 59% vs 37%, respectively), despite an obvious trend.

These trials confirm the benefits of single-agent chemotherapy in elderly patients with advanced NSCLC. A more difficult issue is whether combination chemotherapy is superior in the elderly subset as already demonstrated for younger patients. Although there was a suggestion that the combination of gemcitabine plus vinorelbine was superior to vinorelbine alone in one trial,[21] the Multicenter Italian Lung Cancer in the Elderly Study[22] was a much larger comparison of combination gemcitabine and vinorelbine with the constituent single agents (Table 4). Nearly 700 elderly patients were enrolled. There were no differences in outcome between the single agents and the combination arm, which led the Italian investigators to recommend single-agent therapy as standard for elderly patients.

Table 4—*Chemotherapy in Elderly Patients With Advanced NSCLC

Study/Year	No.	Response Rate, %	MS, mo	1-yr Survival, %
ELVIS[19]/1999				
Vinorelbine	78	20	6.5	32†
BSC	76		4.9	14
Frasci et al[21]/2000				
Gemcitabine plus vinorelbine	76	22	7	30†
Vinorelbine	76	15	4.5	13
Gridelli et al[22]/2003				
Vinorelbine	233	18.4	8.8	41
Gemcitabine	233	17.3	6.6	26
Gemcitabine plus vinorelbine	237	20	7.6	31

*ELVIS = Elderly Lung Cancer Vinorelbine Italian Study Group; MS = median survival time.
†$p < 0.05$.

The experience in the United States is based almost exclusively on retrospective data analyzing and comparing younger (< 70 years old) with older (≥ 70 years old) patients who participated in large, randomized trials that were not necessarily designed to address the elderly issue (Table 5). Because the majority of these trials evaluated platinum-based doublets, it is generally assumed that older patients who entered these trials were considered fit and met the eligibility criteria for enrollment onto the trials. Langer et al[23] analyzed the outcomes of elderly patients in a randomized trial of cisplatin-etoposide vs cisplatin-paclitaxel (ECOG 5592). Approximately 15% of 584 eligible patients were ≥ 70 years. Elderly patients had more leukopenia and neuropsychiatric complications, but efficacy results, including response and survival, were not significantly different compared with the younger cohort. A similar retrospective analysis[24,25] was conducted of the more recent ECOG trial 1594, which randomly assigned 1,139 eligible patients, 20% of whom were ≥ 70 years old, to four different platinum-based regimens. Response rates, survival, and toxicity were similar between the groups. Only nine patients (1%) who entered in this trial were ≥ 80 years old. This subgroup had a much poorer outcome. A similar retrospective analysis was conducted in TAX 326,[26] a phase III trial comparing docetaxel, in combination with either cisplatin or carboplatin, with a reference regimen of cisplatin-vinorelbine. Among > 1,200 patients enrolled, 390 were ≥ 65 years old, the cutoff used for this analysis. Again, elderly patients did as well as younger patients, with no significant difference observed in the efficacy parameters or toxicity end points. Overall, carboplatin-docetaxel had a more favorable therapeutic index. Among the elderly evaluated in this subanalysis, cisplatin-docetaxel, compared with the reference regimen, yielded a statistically significant 3-month improvement in median survival and a consistent benefit in 1-year and 2-year survival rates.

Table 5—*Treatment Outcomes for Elderly Patients With Advanced Stage IIIB/IV NSCLC*

Study/Year	Patients, No.	Subgroups by Age, yr	Survival From Start of Treatment by Age Group			Comments
			Median, mo	1 yr, %	p Value for Effect of Age	
Hensing et al[27]/2003	230	≥ 70	7.1	33	0.65	By treatment arm
		< 70	7.8	30		
Belani et al[26]/2005	1,218	≥ 65	12.6/9.0/9.9	53/39/41	NS	
		< 65	11.0/9.7/10.1	44/37/41		
Langer et al[23]/2002	574	≥ 70	8.5/9.1	29.1	0.29	
		< 70		37.7		
Rocha Lima et al[81]/2002	265	≥ 70	5.7	30	0.63	CALGB 8931 only
		60–69	7.7	26		
		50–59	9.3	28		
Sederholm et al[7]/2005	334	≥ 70	9.4/11	NR	0.2	By treatment arm
		Overall	8.6/10	32/40		
Lilenbaum et al[5]/2005	561	≥ 70	5.8/8.0	1/35	0.546	By treatment arm
		< 70	6.8/9.0	38/33		

*See Table 3 for expansion of abbreviations.

The Cancer and Leukemia Group B (CALGB) performed a randomized trial[5] of carboplatin-paclitaxel vs paclitaxel alone (CALGB 9730). Stratification factors included stage, age, and PS. A total of 155 elderly patients were enrolled, accounting for 27% of the study population. There was no significant difference in response or survival between the elderly and the younger patients. Toxicity was also similar between the two groups, except for a higher incidence of leucopenia in the elderly, but there was no increase in febrile or septic episodes. When results in the elderly subset were analyzed by treatment arm, the nonsignificant difference in survival observed in the general study population was also observed in the elderly subset.

Hensing et al[27] reported an age-based retrospective analysis of a prospective trial that evaluated the optimal duration of therapy in the first-line setting using carboplatin and paclitaxel. In that trial, 29% of patients were ≥ 70 years old. There was no difference in response or survival outcomes or any differences in the rates of hematologic or nonhematologic toxicities seen in the older vs younger patients.

Very little information is available regarding the treatment of patients who have advanced disease and are > 80 years old. Accrual of octogenarians to national trials has been negligible. In the subset analysis[24,25] from ECOG 1594, octogenarians fared substantially worse than patients aged 70 to 79 years when treated with platinum-based combinations (but those who were ≥ 80 years old constituted < 1% of enrollees).

In summary, age alone, at least up to 79 years, should not dictate treatment-related decisions in patients with advanced NSCLC. Elderly patients with a good PS enjoy longer survival and a better QOL when treated with chemotherapy compared with supportive care alone. The single agents vinorelbine, gemcitabine, and docetaxel all are viable options. Elderly patients with good PS and no major comorbid conditions ("fit elderly") seem to benefit from carboplatin-based combination chemotherapy with acceptable toxicity. To date, however, no elderly-specific trial has demonstrated a survival advantage for a doublet compared with a single agent in this setting. Caution should be exercised when extrapolating data for elderly patients (70 to 79 years old) to patients who are ≥ 80 years old. Until more information becomes available, platinum-based chemotherapy cannot be routinely recommended to patients who have advanced NSCLC and are ≥ 80 years old.

Recommendations

3. In patients who have stage IV NSCLC and are elderly (≥ 70 to 79 years old), single-agent chemotherapy is recommended for most. Grade of recommendation, 1A

4. However, in patients who have stage IV NSCLC, are elderly (≥ 70 to 79 years old), have good PS, and lack significant comorbidities, two-drug combination chemotherapy is recommended as an option. Grade of recommendation, 1B

5. In patients who have stage IV NSCLC and are ≥ 80 years old, the benefit of chemotherapy is unclear and should be decided on the basis of individual circumstances. Grade of recommendation, 2C

Is There Evidence That Chemotherapy Benefits Patients With Poor PS?

PS is the most important prognostic factor in advanced NSCLC.[3] Prospective clinical trials and

retrospective analyses[28,29] in the 1980s suggested that patients with stage IV NSCLC and compromised PS experienced substantial toxicity and derived no benefit from systemic chemotherapy. This observation led to the exclusion of patients with a PS of 2 from subsequent cooperative group research. Trials conducted in the late 1990s resumed inclusion of patients with PS of 2 as a subgroup of the overall study population. Arguably as a result of more effective and less toxic chemotherapy, the results demonstrated better tolerability and a trend toward improvement in disease-related symptoms.

CALGB trial 9730,[5] discussed previously, enrolled 99 patients with PS of 2 (18% of the study population). When compared with patients with PS of 0 to 1, who had a median survival of 8.8 months and a 1-year survival of 38%, the corresponding figures for patients with PS of 2 were 3.0 months and 14%, respectively, demonstrating once more the poor prognosis conferred by a lower PS. These differences were statistically significant. However, of importance, when patients with PS of 2 were analyzed by treatment arm, those who received combination chemotherapy had a significantly higher response rate (24% vs 10%), longer median survival (4.7 months vs 2.4 months), and superior 1-year survival (18% vs 10%) compared with those who were treated with single-agent paclitaxel.

ECOG investigators[30] reported a subset analysis of 68 patients with PS of 2 from trial 1594, which randomly assigned > 1,200 patients to four platinum-based regimens. Despite a high incidence of adverse events, including five deaths, the final analysis showed that the overall toxicity experienced by patients with PS of 2 was not significantly different from that experienced by patients with PS of 0 to 1. Efficacy analysis demonstrated an overall response rate of 14%, median survival time of 4.1 months, and a 1-year survival rate of 19%, all substantially inferior to the patients with PS of 0 to 1. The same group of investigators[31] subsequently conducted a phase II randomized trial of attenuated dosages of cisplatin-gemcitabine and carboplatin-paclitaxel in 102 patients with PS of 2. Response rates were 25% and 16%, median survival times were 6.8 months and 6.1 months, and 1-year survival rates were 25% and 19%, respectively. None of these differences was statistically significant, but the survival figures were longer than expected on the basis of historical controls.

Some investigators reported on symptom improvement experienced by patients with PS of 2. Vansteenkiste et al[32] from Belgium compared single-agent gemcitabine with the combination of cisplatin and vindesine in a phase III trial whose primary end point was clinical benefit. Gemcitabine compared favorably to cisplatin and vindesine with longer lasting clinical benefit (16 weeks vs 10 weeks) and no major differences in survival (6.7 months vs 5.5 months). A substantial percentage (20 to 40%) of patients with PS of 2 reported improvement in disease-related symptoms. These findings were similar to those reported by Hickish et al,[33] who concluded that patients with poor PS experienced symptom relief from chemotherapy.

In summary, patients with advanced NSCLC and poor PS represent a sizable component of our practice, yet they have been largely excluded from clinical trials until recently. Although it is unlikely that chemotherapy will eliminate the gap in outcome between patients with PS of 0 to 1 and patients with PS of 2, evidence now suggests that patients with PS of 2 should be offered active treatment. The results of the CALGB subset analysis showed a significant benefit for combination chemotherapy over single-agent therapy in patients with PS of 2. Future trials will need to ascertain the reason for compromised PS and carefully distinguish outcome in those whose functional decline is due to comorbidities vs rapidly advancing malignancy.

Recommendations

6. In patients with stage IV NSCLC and a PS of 2, chemotherapy is recommended on the basis of defined response rates and symptom palliation. Grade of recommendation, 1B

7. In patients with stage IV NSCLC and a PS of 2, no specific recommendation can be given with regard to the optimal chemotherapeutic strategy. A single phase III trial showed a survival benefit to a carboplatin-based doublet compared with a single agent in a prospectively planned subset analysis. Grade of recommendation, 2C

Are There Health-Related QOL Measures That Can Be Used To Predict Outcomes?

Several trials[34–53] have identified patient-reported QOL as a significant prognostic factor for response to therapy, time to progression, and overall survival in patients with NSCLC. A variety of health-related QOL (HRQOL) tools have been used in these trials, although the European Organization for Research and Cancer Treatment Quality of Life Questionnaire (EORTC QLQ-C30), Functional Assessment of Cancer Therapy-Lung (FACT-L), and Functional Living Index-Cancer (FLIC) questionnaires have been the most common. Many of the trials studied heterogeneous patient populations that included patients with other malignancies,[41,49] small cell histology,[43,50] and varying stages of NSCLC.[40,42,43,47,50]

For patients with NSCLC disease, baseline patient-reported QOL has been shown to have prognostic significance for overall survival in patients with early stage disease that was treated with surgery,[47] locally advanced disease that was treated with definitive radiation[48] or combined chemotherapy and radiation,[46] and advanced disease that was treated with chemotherapy alone.[35,36,44,45,53]

Two of these trials[44,47] used the FLIC questionnaire to establish baseline QOL. The first trial[44] studied 40 patients who had advanced NSCLC and were part of a randomized trial to compare best supportive care (BSC) with BSC plus vinblastine and cisplatin. Patients were put into two groups, including those with high baseline FLIC scores (≥ 106.5) and low baseline FLIC scores (< 106.5). The median survival for the high-score group was 24 weeks, compared with 11.9 weeks for the low-score group ($p = 0.03$). In a two-step Cox regression model, baseline FLIC score and marital status were significantly associated with survival ($p = 0.01$ and $p = 0.03$, FLIC score and marital status, respectively). The prognostic significance of the baseline FLIC score was confirmed in a second trial[47] that included a larger patient population (438 patients) enrolled into one of seven trials that were conducted by the Lung Cancer Study Group. Patients with localized and advanced-stage NSCLC, as well as a limited number of patients with small cell disease and mesothelioma, were included in this data set. In a multivariate proportional hazards model, baseline QOL, T status, N status, PS, and small cell histologic features were significantly associated with survival.

Six randomized trials[34–39,52–55] that have compared various treatment regimens for patients with advanced disease have included an analysis of HRQOL measurements and treatment outcomes Two of these trials[52,53] used the FACT-L questionnaire, and both confirmed the prognostic significance of the baseline FACT-L for overall survival. In the ECOG 5592 trial,[53] high baseline scores on the physical well-being and trial outcome index subscales of the FACT-L questionnaire were also significant predictors of both response to treatment and time to disease progression and overall survival. Likewise, in the SWOG 9509 trial,[52] patients with a total FACT-L score of ≤ 98 (median FACT-L score) had a significantly worse survival compared with those with higher scores ($p = 0.003$), and the baseline total FACT-L score remained a significant prognostic factor in the multivariate model even when treatment arm, PS, weight loss ($< 5\%/\geq 5\%$), stage (IIIB/IV), and lactate dehydrogenase were considered. Of the three trials[35,39,52] that used the EORTC QLQ-C30 questionnaire, two trials[35,52] confirmed the prognostic significance of the baseline QOL for survival in multivariate models. In the Multicenter Italian Lung Cancer in the Elderly Study,[52] overall QOL was the most significant prognostic factor for survival in the multivariate analysis ($p = 0.0003$), followed by PS ($p = 0.006$), number of disease sites ($p = 0.02$), and instrumental activities of daily living ($p = 0.04$). Similarly, in the Big Lung Trial,[35] global QOL was a significant prognostic factor in the multivariate model ($p = 0.009$), but other subscales and symptoms were also identified, including role functioning ($p = 0.026$), fatigue ($p = 0.013$), appetite loss ($p = 0.023$), and constipation ($p = 0.0003$). In the third trial[56] that used the EORTC QLQ-C30 questionnaire, QOL subscales including pain ($p < 0.0001$), appetite loss ($p = 0.048$), fatigue ($p = 0.020$), lung cancer symptoms ($p = 0.049$), level of physical functioning ($p = 0.051$), and overall QOL ($p = 0.026$) were significant predictors of survival in the univariate analysis. However, in the multivariate model, only the European Organization for Research and Cancer Treatment pain subscale ($p = 0.020$) added any prognostic information to the clinical factors that were identified (nonadenocarcinoma histology, albumin < 3.5 mg/dL).

Although a number of different questionnaires have been used to establish baseline HRQOL, the results from these larger, randomized trials suggest that patient-reported HRQOL as established by either the FACT-L (physical well-being, trial outcome index, or total FACT-L score) or EORTC QLQ-C30 (global QOL) questionnaire can be used to predict clinical outcomes after treatment with chemotherapy. Furthermore, the data from these trials suggest that HRQOL can provide prognostic information that remains significant when other known prognostic factors are considered, including PS.

Recommendation

8. It is recommended that patient-reported HRQOL be measured using the FACT-L or EORTC QLQ-C30 questionnaire because it is a significant prognostic factor for survival. Grade of recommendation, 1A

Which Factors Should Patients Consider in Choosing Active Treatment Over BSC?

Although it is now clear that survival and QOL of many patients with advanced lung cancer are improved by chemotherapeutic intervention, this treatment course may not be the best choice for all patients. Average survival benefits are modest, with more extended survival occurring in a minority of patients. Survival benefits are also often associated with treatment toxicity. Benefits of chemotherapy in

certain patient groups, such as patients with poor PS or significant comorbid diseases, are less well established. In addition, survival of patients who have advanced disease and do not undergo active treatment seems to have improved in the past decade, further supporting a role for this option in some patients.[57] Studies[58,59] that have investigated patient preferences for active therapy have demonstrated a broad spectrum of individual patient choices regarding active therapy vs BSC that seems unrelated to age, gender, or educational background. Individual preferences not only are based on potential survival benefits but also likely depend on patient attitudes regarding the chances of treatment success, toxicities related to therapy, and short- and long-term effects on overall QOL. Physicians and patients need to understand these factors so that a range of treatment options that are best suited for the patient can be offered.

Most patients want detailed information about their disease. This not only includes disease stage, extent, and expected survival, but also expected disease-related impact on QOL factors that are important to the individual patient. Patient assessments of their own survival time play a large role in their choices regarding treatment planning.[60] However, patients often misunderstand the extent of their disease, which results in inaccurate perceptions regarding treatment goals and survival that are unrecognized or unappreciated by their physicians.[61,62] This phenomenon may be related to physician difficulties explaining a lung cancer diagnosis and prognosis as well as unintended alternative patient perceptions of the information being provided.[60,62,63]

Once armed with individualized knowledge about their cancer, patients should expect a choice of treatment options, understand why their physician has offered these choices, and understand what the goals of each treatment option are. Epidemiologic studies[64,65] of chemotherapy for advanced lung cancer in the United States demonstrate wide variations in treatment patterns that are related to both nonmedical and medical factors. Among medical factors, attitudes of physicians toward various treatment regimens and who should or should not be treated actively are broadly varied and may be influenced by age, PS, associated comorbidities, or knowledge or acceptance of established guidelines.[66,67] Understanding why their physician has chosen these options can help the patient feel more comfortable about the treatments that they will eventually choose.

In addition, careful discussion of the tradeoffs of active treatment to improve survival and overall QOL with the more short-term impact of treatment adverse effects on symptoms and daily activities provides clearer choices for the patient. Retrospective studies[58] in patients who have already received chemotherapy suggest that patient reticence about active chemotherapy may be related to inadequate information regarding therapeutic choices. Specific information related to short- and long-term toxicities, expected beneficial effects of therapy, and treatment risks with regard to the patient's physical and emotional status, in addition to a straightforward explanation of the chances of significant survival improvement, have been welcomed by patients when presented in a structured and understandable manner.[59,68,69] Most patients strongly support receiving a broad array of information about therapeutic choices, and the majority of patients want to participate in decisions regarding therapy to some extent.[58,59,70,71]

Ultimately, decisions regarding active vs supportive treatment are as strongly influenced by personal values, perceived goals for remaining life, social circumstances (*eg*, available support during treatment and illness progression), religious or other spiritual beliefs, and emotional or psychological responses to disease and specific treatment modalities as by potential survival benefits from active treatment. Patients should consider the broad range of information regarding their disease and treatment options in the context of these individualized expectations. One study[72] indicated that patients reported that a majority of physicians provide patients with a general overview of toxicities associated with chemotherapy, although a smaller proportion reported discussion comparing specific toxicities of alternative regimens. However, although a majority of patients are concerned about specific adverse effects, a recent study[73] suggest that the overall effect of changes in QOL on daily physical and social activities may play a larger role in patient perceptions of their sense of well-being rather than specific disease-related symptoms or treatment-related toxicities, suggesting that encouraging a clear understanding of the effects of therapy or BSC on this area by patients and physicians should be emphasized.

Recommendation

9. It is recommended that patients with stage IV NSCLC receive adequate education about the risks and benefits of chemotherapy to enable active participation in the decision-making process regarding treatment selection. Grade of recommendation, 1C

Conclusions

The standard of care for the treatment of the patient with stage IV NSCLC and good PS remains doublet-based therapy, with the exception of patients who are eligible to receive bevacizumab, which has been shown in a large, randomized, phase III trial to improve survival over chemotherapy alone. Elderly patients (≥ 70 to 79 years old) also benefit from therapy, as do patients with poor PS. These populations are heterogeneous, and the optimal approach in these patients remains controversial and should be individualized. The impact of treatment on the extreme elderly (> 80 years old) has not been well documented and requires further study in well-designed clinical trials. Because stage IV NSCLC is not curable, QOL measures should be used to assess treatment benefit because they are patient based and can predict therapeutic benefit. Last, patients should be educated about the nature of their incurable disease and the potential benefit of chemotherapeutic approaches.

Summary of Recommendations

1. In patients with stage IV NSCLC and a good PS, two-drug combination chemotherapy is recommended. The addition of a third cytotoxic chemotherapeutic agent is not recommended because it provides no survival benefit and may be harmful. Grade of recommendation, 1A

2. Bevacizumab improves survival combined with carboplatin and paclitaxel in a clinically selected subset of patients with stage IV NSCLC and good PS (nonsquamous histology, lack of brain metastases, and no hemoptysis). In these patients, addition of bevacizumab to carboplatin and paclitaxel should be considered a therapeutic option. Grade of recommendation, 1A

3. In patients who have stage IV NSCLC and are elderly (≥ 70 years old), single-agent chemotherapy is recommended for most. Grade of recommendation, 1A

4. However, in patients who have stage IV NSCLC, are elderly (≥ 70 years old), have a good PS, and lack significant comorbidities, two-drug combination chemotherapy is recommended as an option. Grade of recommendation, 1B

5. In patients who have stage IV NSCLC and are ≥ 80 years old, the benefit of chemotherapy is unclear and should be decided on the basis of individual circumstances. Grade of recommendation, 2C

6. In patients with stage IV NSCLC and a PS of 2, chemotherapy is recommended on the basis of defined response rates and symptom palliation. Grade of recommendation, 1B

7. In patients with stage IV NSCLC and a PS of 2, no specific recommendation can be given with regard to the optimal chemotherapeutic strategy. A single phase III trial showed a survival benefit to a carboplatin-based doublet compared with a single agent in a prospectively planned subset analysis. Grade of recommendation, 2C

8. It is recommended that patient-reported health-related quality of life be measured using the FACT-L or EORTC QLQ-C30 questionnaire because it is a significant prognostic factor for survival. Grade of recommendation, 1A

9. It is recommended that patients with stage IV NSCLC receive adequate education about the risks and benefits of chemotherapy to enable active participation in the decision-making process regarding treatment selection. Grade of recommendation, 1C

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