Management of Unresectable Locoregionally Advanced and Metastatic Nonsquamous NSCLC

Kimberly A. Bergstrom, PharmD

Developing the right treatment plan for patients with non-small cell lung cancer (NSCLC) depends upon the tumor stage, histologic subtype, patient performance status, predictive tumor markers, and line of therapy. In the setting of NSCLC, where clinical outcomes of chemotherapy regimens are often equivalent and there is a low probability of cure, toxicity and costs become important considerations of care. In this article I outline key considerations regarding treatment options for management of patients with unresectable stage III and stage IV disease.

Management of Unresectable Pathologic Stage IIIA and IIIB Disease

Randomized trials have confirmed that concurrent chemoradiation yields outcomes superior to those obtained with sequential chemoradiation. However, the optimal chemotherapy regimen has not been determined due to a paucity of trials comparing different regimens in the specific setting of stage III disease.

Three phase II trials looked at the outcomes for stage III patients treated with concomitant chemotherapy plus radiation. While these trials are not directly comparable, the clinical outcomes shown for similar patient populations suggest that there may be clinically meaningful differences in important outcomes among different regimens (**Table 1**).

Management of First-Line Metastatic Disease

Patients presenting with disseminated metastases, those with a malignant pleural or pericardial effusion (formerly stage IIIB disease), or those who have relapsed with advanced disease following prior definitive treatment are candidates for palliative systemic chemotherapy. In this setting, studies have shown that the use of combination chemotherapy, particularly in patients with good performance status, can improve survival and is considered the standard of care. The goal of treatment in this setting is to improve survival while minimizing toxicity. To that end, several meta-analyses and large randomized trials have come to the following conclusions:

- Two-drug combination chemotherapy is superior to single agents in terms of response rates and overall survival.[4]
- Not including biologic agents, 3-drug combination therapy generally does not improve overall survival compared with 2-drug combination therapy, but it does significantly worsen toxicity.[4-6]
- Cisplatin therapy yields higher response rates, inconsistent survival benefit, and more toxicity than carboplatin in metastatic NSCLC.[7]
- No single regimen has demonstrated superior survival outcomes in these patients.[8]

Table 2 compares the clinical and toxicity-related outcomes of the main regimens utilized in this setting and studied in randomized phase III trials.

While clinical outcomes do not differ significantly for these regimens, the toxicity-related outcomes, particularly hematologic grade 3 and 4 outcomes, are an important consideration in selecting the best therapy for patients.

Maintenance Therapy After Initial Treatment of Stage IV Disease

Recently, several trials have pointed to the benefits of maintenance therapy after initial treatment of stage IV patients who responded to chemotherapy. While several

PRACTICAL IMPLICATIONS

Developing the right treatment plan for patients with non-small cell lung cancer (NSCLC) depends on assessment of tumor stage, histologic subtype, performance status, treatment intent, and predictive tumor markers.

- In patients with unresectable stage III NSCLC, meaningful survival can be obtained with the use of chemoradiation.
- In patients with stage IV disease, toxicity becomes an important consideration of care.
- In the era of value-based healthcare, efficacy, toxicity, and costs are all important components of formulating an appropriate care pathway.

drugs have been studied in this setting, only erlotinib and pemetrexed are indicated in the maintenance setting following chemotherapy for patients whose disease did not progress during initial therapy. **Table 3** shows the outcomes for these trials. We await overall survival data on 2 of these trials.

Management of Second-Line Metastatic Disease

In the setting of second-line metastatic disease, only 2 chemotherapy agents are approved by the Food and Drug Administration: docetaxel and pemetrexed. These drugs have been compared head to head in this setting and have shown equivalent outcomes in terms of efficacy. In the head-to-head trial, 572 patients treated with 1 prior chemotherapy regimen for advanced/metastatic NSCLC were randomized to docetaxel or pemetrexed every 3 weeks.[9] All patients had good performance status (0-2) and good organ function, and all histologic subtypes were included. A total of 538 patients could be assessed for response, and median follow-up was 7.5 months. The median progression-free survival was 2.9 months for both docetaxel and pemetrexed (hazard ratio [HR] 0.97; 95% confidence interval [CI] 0.82, 1.16; P = .759), while the time to treatment failure was 2.1 months for docetaxel and 2.3 months for pemetrexed (HR 0.94; 95% CI 0.71, 0.997; P = .046). The median overall survival was 7.9 months for docetaxel and 8.3 months for pemetrexed (HR 0.99; 95% CI 0.82, 1.2; P = .226).

While the trial showed no differences in clinical outcomes or quality of life, there were some meaningful differences in toxicity, use of supportive care, and hospitalization rates favoring the use of pemetrexed (**Table 4**).

Cost of Therapy

As we move toward value-based care, it is important to consider the cost of care when the quality of care (efficacy/toxicity) is difficult to distinguish among regimens. While many of the drugs used to treat NSCLC are generically available, there are still considerable differences in costs, ranging from approximately $3300 to $33,000 based on Medicare reimbursement for 3 months of therapy (**Table 5**).

Conclusions

Developing the right treatment plan for NSCLC patients depends on a thorough assessment of the tumor stage, histologic subtype, performance status, treatment intent, and predictive tumor markers. Understanding the clinical and toxicity-related outcomes of contemporary, randomized phase III trials in the treatment setting (initial treatment of stage III disease vs first-line or second-line metastatic treatment) in which care is contemplated can help clinicians formulate a care pathway that thoroughly focuses on clinical evidence and cost. In the setting of unresectable stage III NSCLC, meaningful survival can be obtained with the use of chemoradiation. In 3 trials that looked specifically at stage III patients, overall survival of up to 22 months was achieved with carboplatin-pemetrexed-radiotherapy treatment. In the setting of stage IV disease, where clinical outcomes of chemotherapy regimens are often equivalent and there is a low probability of cure, toxicity becomes an important

Table 1. Clinical Outcomes of Concomitant Chemotherapy-Radiotherapy Regimens in Patients With Stage III NSCLC

Regimen	Patient Characteristics	Overall Response Rate	Median Progression-Free Survival, mo	Median Overall Survival, mo
Carbo-pemetrexed-RT[1]	Previously untreated, unresectable pathologic stage III NSCLC; PS: 0-1	73%	12.9	22.3
Cisplatin-etoposide-RT[2]	Previously untreated, unresectable pathologic stage IIIB NSCLC; PS: 0-1	NR	NR	15
Carbo-paclitaxel-RT[3]	Previously untreated, unresectable stage IIIA, IIIB NSCLC; Karnofsky PS: ≥70%	NR	8.7	16.3

Carbo indicates carboplatin; NR, not reported; NSCLC, non-small cell lung cancer; PS, performance status; RT, radiotherapy treatment.

Table 2. Clinical and Toxicity-Related Outcomes of Randomized Phase III Trials in First-Line Metastatic NSCLC

Regimen Name	ORR	Median TTP/PFS	Median OS	1-Year OS	Neutropenia/FN Grade 3/4	Anemia Grade 3/4	Thrombocytopenia Grade 3/4	Other Grade 3/4 Toxicities
Cisplatin-pemetrexed[10]	30.6%	PFS 4.8 mo	10.3 mo (12.6 mo in patients with adenocarcinoma)	43.5%	Neutropenia 15% FN 1%	6%	4%	Use of GCSF 3% Fatigue 6.7%
Cisplatin-vinorelbine[11,12]	24.5%-39.2%	TTP 5-5.3 mo	9.7-10.1 mo	40.8%-41%	Neutropenia 37%-79% FN 4.5% Infection 7.8%	6%-24%	3.8%-6%	Nausea 15%-16% Neurotoxicity 4%-11%
Cisplatin-docetaxel[12]	31.6%	TTP 5.1 mo	11.3 mo	46%	Neutropenia 75% FN 4.9% Infection 8.4%	6.9%	2.7%	Nausea 9.9% Asthenia 12.7%
Carbo-docetaxel[12]	23.9%	4.6 mo	9.4 mo	38%	Neutropenia 74.4% FN 3.7% Infection 11%	10.5%	7%	Asthenia 11% Pulmonary 13.5%
Carbo-gemcitabine[13]	42%	PFS 5.3 mo	10 mo	40%	Neutropenia 34% Infection 8%	9%	24%	
Cisplatin-irinotecan[14]	31%	NR	13.9 mo	59.5%	Neutropenia 84% FN 14%	31%	6%	Diarrhea 16% Anorexia 35% Fatigue 13% Nausea 29% Vomiting 13%
Carbo-paclitaxel[15]	10%	PFS 4.5 mo	10.3 mo	44%	Neutropenia (Gr 4) 16.8% FN (1 Gr 5 event) 2%	0.9% Gr 4	0.2% Gr 4	1 patient with Gr 5 GI bleed
Carbo-paclitaxel-bevacizumab[15]	27%	PFS 6.2 mo	12.3 mo	51%	Neutropenia (Gr 4) 25.5% FN (5 Gr 5 events) 5.2%	0% Gr 4	1.6% Gr 4	5 Gr 5 hemoptysis events 2 Gr 5 hematemesis events
Carbo-pemetrexed[16] (22% of patients with PS 2)	NR	NR	7.3 mo	34%	Neutropenia 40% Infection 8% Gr 5 infection 1%	13%	24%	Use of FGS 1% Use of ESA 1%
Docetaxel-gemcitabine[11]	30%	TTP 4 mo	9 mo	34.3%	Neutropenia 17% FN NR	2%	4%	Diarrhea 6% Neurotoxicity 6%
Pemetrexed maintenance[17]	51.7% (includes stable disease)	PFS 4.3 mo	13.4 mo (15.5 mo in patients with nonsquamous cell lung cancer)	NR	Neutropenia 2.9%	3%	0%	Fatigue 5%

Carbo indicates carboplatin; ESA, erythropoiesis-stimulating agent; FN, febrile neutropenia; GCSF, granulocyte colony-stimulating factor; GF, growth factor; GI, gastrointestinal; Gr, grade; NR, not reported; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall response; PFS, progression-free survival; PS, performance status; TTP, time to progression.

consideration of care. Finally, in the second-line metastatic setting, both docetaxel and pemetrexed have equivalent clinical outcomes; however, pemetrexed as a single agent is statistically superior to docetaxel in terms of rates of grade 3/4 neutropenia and febrile neutropenia–related toxicities, including hospitalization rates for febrile neutropenia. In the era of value-based healthcare, efficacy, toxicity, and costs are all important components of formulating an appropriate care pathway.

Author Affiliation: From University of California, San Francisco, CA; and McKesson Specialty Care Solutions, San Rafael, CA.

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Table 3. Maintenance Regimens in Stage IV NSCLC Patients Whose Disease Did Not Progress During Initial Treatment

Regimen	Overall Response Rate	Median Progression-Free Survival	Median Overall Survival
Pemetrexed maintenance[17]	51.7% (includes stable disease)	4.3 mo	13.4 mo (15.5 mo in patients with nonsquamous cell lung cancer)
Erlotinib maintenance[18]	40.8% (includes stable disease)	3.75 mo (HR = 0.71; *P* <.0001)	NR
Cisplatin-vinorelbine-cetuximab f/b cetuximab maintenance[19]	36% (does not include stable disease)	4.8 mo (HR = 0.93; *P* = .39)	11.3 mo (HR = 0.871; *P* = .044)
Bevacizumab + chemotherapy f/b bevacizumab + erlotinib or bevacizumab alone[20]	NR	4.8 mo (bevacizumab + erlotinib) vs 3.7 mo (bevacizumab alone) (HR = 0.722; *P* = .0012)	NR

f/b indicates followed by; HR, hazard ratio; NR, not reported; NSCLC, non-small cell lung cancer.

Table 4. Pemetrexed Versus Docetaxel Toxicity Outcome Results in Second-Line Therapy for Metastatic NSCLC

	Rates of Grade 3/4 Toxicities, Hospitalizations, and Use of Supportive Care, %		
Event	Pemetrexed Patients (n = 265)	Docetaxel Patients (n = 276)	*P*
Neutropenia	5.3	40.2	<.001
Febrile neutropenia	1.9	12.7	<.001
Anemia	4.2	4.3	.99
Thrombocytopenia	1.9	0.4	.116
≥1 Hospitalization for febrile neutropenia	1.5	13.4	<.001
≥1 Hospitalization for any other drug-related adverse event	6.4	10.5	.92
Use of ESAs/RBC transfusions	6.8/16.6	10.1/11.6	.1078

ESA indicates erythropoiesis-stimulating agent; NSCLC, non-small cell lung cancer; RBC, red blood cell.

Table 5. Non-Small Lung Cancer Regimen Costs[a]

Regimen name	Cost per Regimen to Medicare, $
Carboplatin (AUC 5) D1-gemcitabine (1200) D1,8 q 21 d	17,409.27
Carboplatin (AUC 5) D1-pemetrexed (500) D1 q 21 d	32,375.37
Carboplatin (AUC 6) D1-docetaxel (75) D1 q 21 d	11,911.50
Carboplatin (AUC 6) D1-paclitaxel (200) D1 q 21 d	3297.12
Carboplatin (AUC 6) D1-paclitaxel (200) D1-bevacizumab (15) D1 q 21 d	29,322.07
Cisplatin (75) D1-docetaxel (75) D1 q 21 d	12,075.05
Cisplatin (75) D1-pemetrexed (500) D1 q 21 d	16,081.43
Cisplatin (80) D1-irinotecan (60) D1,8,15 q 28 d	5018.27
Cisplatin (80) D8-vinorelbine (30) D1,8 q 21 d	4885.70
Docetaxel (75) D1 q 21 d	8153.12
Docetaxel (85) D8-gemcitabine (1000) D1,8 q 21 d	25,722.34
Pemetrexed (500) D1 q 21 d	20,411.26
Average cost per patient	15,555.21

AUC indicates area under the curve; q, every.
[a]From the Medicare fee schedule, first quarter 2011. Regimens are used in first-line and second-line metastatic settings. Regimens include costs of chemotherapy/biologic drugs, supportive care medications (antiemetics, premedications), drug administration costs, lab costs (complete blood count, chemistry panel), and Evaluation and Management visit costs for 3 months of therapy. These costs do not include costs of hospitalizations or use of growth factors.

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Address correspondence to: Kimberly A. Bergstrom, PharmD, Chief Clinical Officer, McKesson Specialty Care Solutions US Oncology, 4040 Civic Center Dr, Ste 225, San Rafael, CA 94903. E-mail: kim.bergstrom@mckesson.com.

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