Systemic Therapy Options for Non-Small-Cell Lung Cancer in Patients with a Poor Performance Status

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Continuing Medical Education Information

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About the Activity
This activity is based on a brief article developed as part of the E-Update Series and posted on the Web. The series is geared to oncologists and addresses new treatments of cancer or modifications thereof.
This activity has been developed and approved under the direction of Beam Institute.

Activity Learning Objectives
After reading this article, participants should be able to:

- Discuss appropriate management strategies for patients with advanced non-small cell lung cancer (NSCLC) who have a poor performance status (PS).
- Explore the role of concurrent chemotherapy for locally advanced NSCLC in patients with a PS of 2.
- Review the single-agent, doublet, and molecularly targeted therapies under investigation for patients with advanced NSCLC with a poor PS.
- Appreciate the need for enrolling patients in the PS2 population in well-designed clinical trials.

Target Audience
This activity targets physicians in the fields of oncology and hematology.

Accreditation
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Introduction
Although significant advances have been made in the systemic therapy of non-small-cell lung cancer (NSCLC) in patients with a good performance status (PS), the subgroup of patients with a poor PS has not been studied as well. Current guidelines are based primarily on extrapolation from other populations and small subgroup analyses of larger trial populations, with remarkably few direct data to shape treatment decisions. With cisplatin-based doublet chemotherapeutic regimens as a historic standard of care for patients with advanced NSCLC, those with a PS of 2 or higher on the Zubrod/ECOG (Eastern Cooperative Oncology Group) Scale (Table 1) were largely excluded from clinical trials on the basis of the presumption that they could not tolerate the toxicities of such aggressive systemic therapies.
In recent years, however, systemic therapeutic options have become incrementally less toxic. Substitution of carboplatin for cisplatin in doublet regimens and introduction of the “third” generation of chemotherapeutic agents (vinorelbine, gemcitabine [Gemzar], paclitaxel, docetaxel [Taxotere], and pemetrexed [Alimta]) have made it possible to administer combination chemotherapy regimens in patients with advanced NSCLC and a poor PS. Finally, targeted therapies such as the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) gefitinib (Iressa) and erlotinib (Tarceva) have emerged as particularly attractive options that might offer a survival benefit without the toxicities associated with conventional chemotherapy.

The study of patients with a poor PS and cancer in general, or NSCLC in particular, has been evolving rapidly over the past several years. Until just a few years ago, there were remarkably few studies dedicated to elderly and/or frail patients with NSCLC. Over the past 5 to 6 years, several trials emerged that focused initially on elderly patients (usually defined as 70 years or older), but these trials still disproportionately enrolled older patients with a favorable PS. More recently, studies have targeted a population of patients who are either elderly or who have a PS of 2. These studies have consistently demonstrated that patients with a poor PS have a far worse overall survival (OS) than older patients with a good PS, highlighting that PS is far more predictive of outcome than chronologic age. Only in the past few years have studies that specifically focus on NSCLC patients with a PS of 2 been initiated; it is now recognized that this distinct subpopulation cannot be readily aggregated with elderly patients. Although some of our conclusions may be gleaned from subset analyses of PS2 patients from larger studies that primarily included patients with a good PS, there is the significant possibility of a selection bias that preferentially included PS2 patients capable of tolerating treatment protocols designed for patients with a favorable PS.

Prospective trials designed for patients with NSCLC who have a poor PS are critically important to improve the outcomes in this population. This review will focus on the appropriate management of patients with advanced NSCLC who have a poor PS. There are only very limited data on the role of adjuvant therapy in patients with resected NSCLC who have a poor PS at the time of evaluation for adjuvant therapy. They account for only 3% to 7% of the overall population in adjuvant chemotherapy studies. These trials have generally demonstrated a nonsignificant trend or significantly adverse outcomes with chemotherapy in PS2 patients. Other studies of platinum-based adjuvant chemotherapy have largely excluded patients with a PS of 2 or had such small numbers that they were not evaluated separately.

One particular adjuvant chemotherapy trial, ANITA-2, was focusing specifically on patients with a poor PS and on those who have contraindications to receiving cisplatin. This trial was randomizing patients with stage IB to IIIA resected NSCLC to receive vinorelbine as a single agent for 16 weeks or observation alone, potentially also including postoperative radiotherapy (RT) at the discretion of the treating site. Unfortunately, this phase III trial was terminated early because of poor accrual.
Based on the limited data, I am reluctant to recommend adjuvant chemotherapy for PS2 patients with NSCLC.

Approaches for Locally Advanced Disease

Similar to the situation for earlier stage, resectable NSCLC, the vast majority of clinical trials for aggressive, combined-modality approaches of chemotherapy and radiation therapy have often been restricted to patients with a good PS. Chemoradiation approaches, and especially those that include concurrent chemotherapy and thoracic RT, are generally accompanied by considerable acute toxicities and a treatment-related death rate in the 5% to 6% range, even in fit patients, thereby precluding those with marginal PS at baseline from participating in more rigorous multimodality strategies.

The Southwest Oncology Group (SWOG) conducted a phase II study (SWOG 9429) of an attenuated chemotherapy regimen given concurrently with RT for “poor-risk” patients. Poor risk was defined as a PS of 2 with a low albumin level or >10% weight loss, insufficient pulmonary reserves for more aggressive combined therapy (FEV1 [forced expiratory volume in one second] of less than 2.0 L but at least 1.0 L), or comorbidities precluding administration of standard cisplatin (including hearing loss, renal insufficiency, congestive heart failure, or peripheral neuropathy). Patients enrolled in this study received attenuated doses of carboplatin and etoposide for a total of 2 cycles concurrently with daily thoracic RT to 61 Gy.

This trial demonstrated this approach to be feasible, with moderate acute toxicity and no treatment-related deaths. It also showed encouraging efficacy, with a median OS of 13 months and a 2-year OS of 21%. However, the majority of enrolled patients had a good PS and compromised pulmonary function, with only 18% of enrolled patients having a PS of 2. I am impressed by the benefits of concurrent chemotherapy for locally advanced NSCLC and generally pursue a carboplatin-based approach with concurrent definitive RT without consolidation systemic therapy.

A follow-up trial, SWOG 9712, evaluated the same poor-risk population treated with the same concurrent chemoradiation approach as in SWOG 9429 but added 3 cycles of consolidation paclitaxel. Unfortunately, there were four treatment-related deaths during the concurrent chemoradiation therapy and another four during the consolidation phase with paclitaxel. The median survival was 10.1 months, with a 2-year survival rate of 25%. The authors concluded that there was no evidence that consolidation therapy with paclitaxel improved survival but there was concern that it conferred prohibitive toxicity.

More recent studies have attempted to assess whether targeted therapies, such as those directed against EGFR, may provide a systemic therapeutic benefit comparable to standard chemotherapy when administered concurrently with thoracic RT for poor-risk patients with locally advanced NSCLC. The Cancer and Leukemia Group B (CALGB) investigators reported on a treatment protocol in which all patients were started with induction carboplatin/paclitaxel for 2 cycles every 3 weeks along with the oral EGFR TKI gefitinib. Investigators then gave concurrent chemoradiation therapy and gefitinib for patients with a good PS and gave gefitinib alone without chemotherapy during definitive thoracic RT for PS2 patients.

The trial closed early, based on emerging negative results with gefitinib. A total of 20 patients on the poor-PS stratum were enrolled, for whom the failure-free survival was 11.5 months, 1-year OS was 60%, and median OS was 19.0 months. These efficacy results were actually superior to those for the patients with a good PS, but the small numbers did not allow any significant conclusions to be drawn, except that further study of EGFR inhibitor therapy combined with definitive RT in PS2 patients is warranted.

Apparently, subsequent trials have not yet been undertaken with gefitinib or other EGFR inhibitors in this setting. At the present time, there are insufficient data to recommend the use of EGFR inhibitors in conjunction with RT in locally advanced NSCLC (regardless of PS) outside the context of a clinical trial.

Chemotherapy

The role of chemotherapy in patients with a poor PS and metastatic NSCLC compared with those with early-stage and locally advanced NSCLC has been addressed. Several different approaches have been studied, including the role of single-agent chemotherapy, carboplatin-based doublets, nonplatinum-containing doublets, and molecularly targeted therapies. Cisplatin-based doublet chemotherapy has been largely eschewed for the PS2 population, after the seminal ECOG 1594 trial included PS2 patients and then subsequently amended the trial to exclude this population after a preliminary analysis suggested an excessive number of early deaths among these patients. A
subsequent, more detailed analysis, however, indicated that the majority of these deaths were related to comorbidities and underlying cancer rather than the treatment itself. Nevertheless, the increasing study of PS2 patients with advanced NSCLC has coincided with a growing array of treatment options that are generally less challenging in terms of potential toxicity than cisplatin doublet combinations.

As previously noted, much of the early work that raised interest in the marginal PS patient population was focused primarily in the elderly population, which included some patients with a PS of 2 and significant comorbidities. After initial work demonstrated a survival benefit for single-agent vinorelbine in an elderly population that included many poorer risk patients, Hesketh and colleagues launched a single-arm phase II trial for elderly or PS2 patients with advanced NSCLC. Treatment consisted of single-agent vinorelbine as first-line therapy for 3 cycles, followed by sequential weekly docetaxel for 3 of 4 weeks for up to 3 cycles. This study demonstrated markedly superior survival in the fit elderly compared with the poor PS population; the median OS was 9.1 and 5.5 months, and 1-year OS was 41% and 13%, respectively.

In addition to these studies, other single-arm phase II trials have demonstrated the feasibility of pursuing other monotherapy approaches with a wide range of single agents, including the taxanes, gemcitabine, vinorelbine, or pemetrexed in elderly and/or PS2 patients. These trials have generally demonstrated comparable results and have consistently revealed that PS, rather than advanced age, is associated with a worse OS and ability to tolerate treatment as planned. As these are relatively small single-arm trials, no agent or regimen has emerged as a real standard, with a wide range of more or less comparable results.

Paclitaxel poliglumex, an investigational, novel formulation of paclitaxel, has also been studied in two separate randomized phase III trials in the PS2 population. The new agent has not been shown to have superior efficacy to the comparator chemotherapy options (vinorelbine or gemcitabine monotherapy in one trial, carboplatin/paclitaxel in the other) in the overall trial population and is not commercially available at the present time.

Several recent trials have compared monotherapy with doublets in the poor PS population. Similar to the ELVIS trial, the Multicenter Italian Lung Cancer in the Elderly Study (MILES) compared monoagent therapy with vinorelbine or gemcitabine alone with a combination in both an elderly (> age 70) population (N = 698) that included 20% PS2 patients (Figure 1). The combination demonstrated no superiority in efficacy in terms of response rate or median or 1-year OS, but it was associated with more adverse effects.

![Figure 1. An algorithm to assist in decision-making regarding chemotherapy for older patients](Click to enlarge)
In contrast, the CALGB 9730 trial, conducted by Lilenbaum and colleagues,\(^ {11}\) enrolled a general advanced NSCLC population (N = 561), including 18% with a PS of 2. Patients were randomized to receive carboplatin/paclitaxel or paclitaxel alone every 3 weeks. The doublet showed a nonsignificant benefit in OS for the entire trial population; a prospectively planned subset analysis of the 99 PS2 patients revealed that although these patients had a much worse survival than patients with a good PS, PS2 patients who received the carboplatin/paclitaxel doublet had a significantly better OS and more than twice the response rate compared with PS2 recipients of paclitaxel monotherapy.

In addition, several other smaller trials comparing single-agent and carboplatin doublets have also been performed; they have demonstrated trends toward superior response rate, progression-free survival (PFS), and sometimes OS in PS2 recipients of doublets compared with single-agent approaches. In another randomized trial of 350 elderly or PS2 patients who received either weekly docetaxel or docetaxel with gemcitabine,\(^ {12}\) PFS was significantly superior for the combination (4.8 vs 2.9 months; \(P = 0.004\)), but there were no significant differences in OS.

Although some of the data presented here suggest it is feasible to administer doublet therapy (predominantly carboplatin based) in patients with a PS of 2, single-agent chemotherapy continues to be the appropriate choice for this subgroup of patients. My approach to PS2 patients with advanced NSCLC is to administer carboplatin-based doublet chemotherapy for those who wish to maximize the efficacy of treatment; for PS2 patients who are wary about chemotherapy-related toxicity, I prefer to use single-agent chemotherapy.

**Targeted Therapies**

The finding that erlotinib can produce a survival benefit with relatively mild toxicity in previously treated patients with advanced NSCLC has led to considerable interest in treating patients with a poor PS. One recent single-arm trial, conducted by Hesketh and colleagues,\(^ {13}\) administered erlotinib as a single agent to 73 PS2 patients and revealed overall results comparable to those with single-agent chemotherapy.

As a follow-up to the CALGB 9730 trial that demonstrated the feasibility of carboplatin/paclitaxel, and the emerging appeal of erlotinib as a potentially effective nonchemotherapy alternative for the PS2 patient population, Lilenbaum and colleagues conducted a randomized phase II trial that directly compared the doublet chemotherapy with erlotinib in 103 previously untreated PS2 patients with advanced NSCLC.\(^ {14}\) In this study of patients not selected on the basis of either clinical or molecular characteristics associated with a favorable response to erlotinib, chemotherapy was associated with a superior overall response rate (12% vs 2%), DCR (disease control rate [responses and stable disease]; 53% vs 39%), median PFS (3.5 vs 1.9 months), and median OS (9.7 vs 6.6 months). Part of the inferior survival seen with initial assignment may have been due to the fact that crossover to second-line erlotinib was planned at the time of disease progression for recipients of initial carboplatin/paclitaxel and that relatively few patients on initial erlotinib received subsequent therapy. Quality of life was not clearly different with either treatment. The results from this small but notable randomized phase II trial strongly suggest that chemotherapy is associated with improved efficacy compared with EGFR inhibitor therapy, at least in an unselected population.

Turning to a different targeted therapy, CALGB trial 30402 explored the safety and feasibility of combining weekly docetaxel with either the monoclonal antibody agonist EGFR cetuximab (Erbitux) or the proteasome inhibitor bortezomib (Velcade) in 55 PS2 patients.\(^ {15}\) Response rates in the 10% to 15% range were seen on both arms, and PFS and OS results overall were relatively disappointing with both combinations. Given these findings and a few treatment-related deaths on both arms, neither option will be pursued further by the CALGB.

More work needs to be done to understand how best to manage patients with a poor PS. The initial trials focused on the combined population of elderly or PS2 patients, consistently demonstrating markedly superior results for older patients with a good PS compared with poor-risk patients of any age. Only the most recent clinical trials have been prospectively dedicated exclusively to the PS2 population. These studies have demonstrated the feasibility of treating such patients to achieve clinical benefit, either with one of many feasible monoagent chemotherapy regimens or with a carboplatin-based doublet. Thus far, targeted therapies, either as a replacement for or combined with standard chemotherapy, have not been shown to produce greater efficacy or a more favorable therapeutic index. Although we do not yet have firm guidelines for PS2 patients at any stage of NSCLC, the overall disappointing results for the PS2 population underscore the need for enrolling patients in well-designed clinical trials.