



Eric Roeland, MD

Eric Roeland, MD, is from the UC San Diego Moores Cancer Center in La Jolla, California.



Charles Loprinzi, MD

Charles Loprinzi, MD, is from the Mayo Clinic in Rochester, Minnesota.

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In Chemotherapy for Lung Cancer, Sometimes Less is More

Eric Roeland, MD; Charles Loprinzi, MD; Timothy J. Moynihan, MD; Thomas J. Smith, MD; and Jennifer Temel, MD

Chemotherapy remains the backbone of care for patients with metastatic cancer and provides increasing hope for patients and their families as novel drug targets and therapeutic agents are discovered. Over the past decade, the therapeutic arsenal has markedly expanded, from nitrogen mustard and folic acid antagonists of the mid-20th century to the targeted regimens of “personalized” medicine today. In patients with metastatic disease, chemotherapy can slow disease progression, leading to prolonged survival, and palliate symptoms. Lung cancer remains the leading cause of cancer-related mortality in the United States because of both the high prevalence of advanced disease at diagnosis and the low rate of cure of early-stage disease. Thus, many patients with metastatic non–small cell lung cancer (NSCLC) receive chemotherapy with the goal of prolonging life, relieving symptoms, and improving quality of life (QOL).

Although chemotherapy can achieve these goals in selected patients with metastatic NSCLC and a good performance status (PS), it has a limited role in patients whose cancer has progressed through multiple lines of therapy and those with a poor PS (eg, ECOG 3 or 4). The response rates for patients with metastatic NSCLC treated with both a platinum and a taxane have been reported to be only 2% for third-line and 0% for fourth-line chemotherapy,¹ which is insufficient to provide a significant survival benefit.² Data regarding patients with NSCLC with a PS of 2 remains an unsolved issue, and carefully designed phase III trials are necessary to better define optimal treatment for patients with a borderline PS.^{3–5} Thus, ASCO and NCCN guidelines have concluded that patients with a PS greater than 3 do not benefit from chemotherapy, except erlotinib for epidermal growth factor receptor mutation–positive patients and crizotinib for ALK–positive patients.^{6–8} Despite these published national guidelines, the current trend is for patients with metastatic NSCLC to receive multiple lines of chemotherapy, even in the face of a declining or poor PS.^{9–12}

The continued discoveries of novel, targeted therapies are making it increasingly more challenging for patients and oncologists to forgo additional treatment, because of the hope of finding one that will lead to long-term progression-free survival. We all hope that the next erlotinib or crizotinib is on the horizon and that we will have effective targeted therapies available for all patients with metastatic NSCLC. This hope makes it difficult for oncologists to not offer that “one additional treatment” when faced with a patient whose condition is declining.

However, the downside to this eternal optimism is that patients may receive additional lines of therapy with no clear benefit and with real potential harm. Although data have not conclusively demonstrated that prolonged chemotherapy may truly harm or even decrease survival in patients with metastatic cancer, one study examining Medicare patients with congestive heart failure or any 1 of 5 different malignancies supported the theory that hospice referral led to an improved survival,¹³ and another study examining continued chemotherapy to the pre-mortem period suggested that it only delays hospice referral and does not improve survival.¹⁴

A recently conducted prospective, randomized, single-institution clinical trial provides important insight into the question of prolonged chemotherapy administration in patients with incurable NSCLC.¹⁵ In this study, 151 patients with

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newly diagnosed metastatic NSCLC were randomized to receive early palliative care integrated with standard oncology care versus standard oncology care alone. Either a board certified palliative care physician or an advanced practice nurse was scheduled to evaluate patients assigned to the early palliative care arm within 3 weeks of initial diagnosis and at least monthly thereafter. These visits entailed a focused physical examination, psychosocial and spiritual history, symptom and functional status assessment, and continual reevaluation of goals of care, per the National Consensus Project for Quality Palliative Care guidelines.¹⁶ The primary outcome of the trial was comparison of QOL at 12 weeks between study arms. Patients in both arms underwent standard cancer care and therapy per their primary oncologist's discretion.

Patients assigned to receive early, integrated palliative care experienced an improved QOL and lower rates of depression at 12 weeks. Unexpectedly, patients assigned to early palliative care had a 2.7-month survival benefit.¹⁵ This finding rivals survival prolongations with standard first-line metastatic NSCLC chemotherapy regimens. For example, this survival benefit is comparable to that seen with cytotoxic agents in patients in similar settings: 2 months for bevacizumab when added to carboplatin/paclitaxel and 2.6 months for maintenance pemetrexed.^{17,18} Although the possibility of prolonged survival with supportive care interventions has been shown in several earlier studies,^{19,20} the statistically significant survival benefit has been debated and criticized as an isolated phenomenon.

A secondary analysis of this study evaluated chemotherapy administration in the final months of life for the patients who died within an 18-month follow-up period (n=133; 78% in the early palliative care arm vs. 88% in the standard oncology arm).²¹ The number of chemotherapy regimens did not differ significantly by study group. However, patients in the early palliative care group were half as likely to receive intravenous chemotherapy within 60 days of death (odds ratio, 0.47; 95% CI, 0.23–0.99; $P=.05$), and experienced a longer interval between the last dose of intravenous chemotherapy and death (median, 64 vs. 41 days; $P=.02$). No difference was seen in the use of oral agents, such as erlotinib, in the last months of life. Consistent with other studies, the cost of care was lower at the end of life in the palliative care arm.²¹

Is it possible that the lower rates of intravenous chemotherapy administration near the end of life contributed to the survival benefit seen in this study? Patients who have already received multiple prior lines of chemotherapy generally have a poorer PS than those with newly diagnosed disease. In addition, intravenous chemotherapy certainly has associated toxicities, such as immune suppression and end-organ damage, which may contribute to a shortened survival. Given this information, it is reasonable to suspect that prolonged chemotherapy administration in the advanced metastatic solid tumor setting may have an adverse effect on overall survival. The response rates to conventional chemotherapy in the third and fourth line are low, 17% and 11%, respectively,²² compared with 2% and 0% in patients who underwent prior treatment with a taxane and platinum drug.²³ No randomized trials exist of best supportive care with or without nth-line chemotherapy, but a 20% response rate has been the threshold when a survival advantage has been observed²⁴; it is likely that toxicity outweighs any small benefit. When studied, chemotherapy in NSCLC given within 2 weeks of death was not associated with any survival benefit,²⁵ whereas hospice was.²⁶ However, there are other possible factors that may have contributed to the survival advantage in this trial, including improved control of symptoms and earlier use of hospice. Additional research is needed to sufficiently answer this important and timely question.

One reason patients may receive potentially futile chemotherapy near the end of life is that oncologists often reluctant to initiate conversations with patients regarding their prognosis and goals of care. These conversations not only are emotionally difficult for physicians and nurses, but also can be time-consuming. Data suggest that only a



Timothy J. Moynihan, MD

Timothy J. Moynihan, MD, is from the Mayo Clinic in Rochester, Minnesota.



Thomas J. Smith, MD

Thomas J. Smith, MD, is from The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, Maryland.

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Jennifer Temel, MD

Jennifer Temel, MD, is from Massachusetts General Hospital, Boston, Massachusetts.

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minority of patients with metastatic NSCLC engage in conversations with oncologists regarding prognosis and end-of-life care preferences.^{27,28} Physicians also tend to overestimate survival times in patients with metastatic cancer and prefer to wait until no more treatment options remain to have conversations about goals of care. This likely contributes to the administration of chemotherapy close to time of death.^{29–32}

Despite our good intentions, more chemotherapy at the end of life may not prolong life—rather, it may hasten death. A hypothetical example of this concept is shown in Figure 1, which illustrates the decreasing benefit of chemotherapy on life expectancy in advanced NSCLC. Although oncologists understand that chemotherapy leads to net harm in patients who are completely bedridden, when this net harm begins is not clear. A better understanding of this issue, through additional research efforts in palliative and end-of-life care, is necessary to address this concerning trend. Sometimes, less may be more.

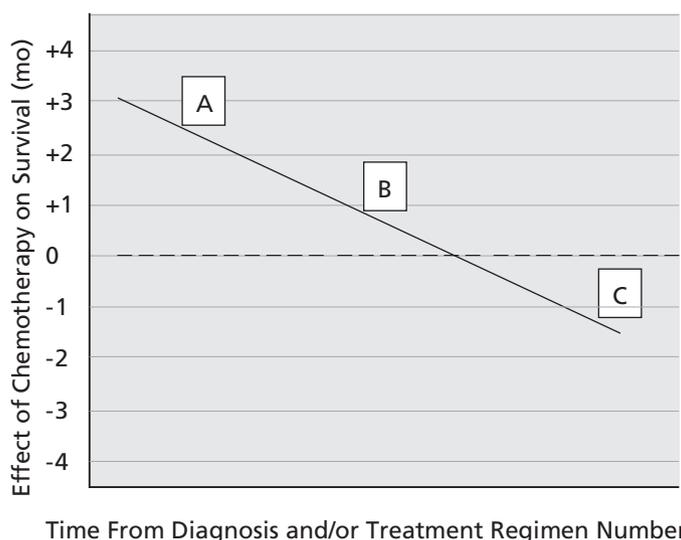


Figure 1 The hypothetical benefit of chemotherapy on life expectancy, showing the benefit seen with early disease treatment for cancers such as non–small cell lung cancer (A). This benefit lessens with treatments for more advanced disease (B) and then leads to net harm as the disease progresses and becomes more resistant to chemotherapy (C).

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