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The Need to Prioritize and Re-prioritize Palliative Care Options: Smoking Cessation as a Case-in-Point

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Opinion statement

Palliative care in cancer patients requires a continuous reprioritization of effort. This review describes the need for this reprioritization and uses smoking cessation as a case-in-point. The treatment of patients with metastatic non-small cell lung cancer has changed dramatically in the past few years. Interestingly, patients who had previously smoked now have an improved prognosis—for a variety of reasons. This review discusses this last observation in detail and raises the question of how forcefully we should advise smoking cessation in patients with incurable metastatic non-small cell lung cancer.

Introduction

Palliative care has become an integral part of cancer care including the care of lung cancer patients. As recently reviewed in a meta-analysis from Fulton and others, palliative care appears to improve both quality of life and, at times, overall survival for patients with cancer [1]. In an often-cited trial, Temel and others showed the

potential for a survival benefit [2]. These investigators randomly assigned patients with metastatic lung cancer to either chemotherapy plus palliative care consultation versus chemotherapy alone. Interestingly, despite the fact that patients assigned to the chemotherapy alone group were allowed to receive a palliative care consultation at a later date, this trial showed that patients assigned palliative care up front lived longer: 11.6 months versus 8.9 months, $p = 0.02$. Although this study did not examine survival as its primary endpoint and although the benefits of a palliative care consultation go beyond the demonstration of a survival advantage, these tentative findings serve to further highlight the importance of integrating palliative care into general cancer care, an approach that has justifiably acquired widespread acceptance. This study also raises several questions on the definition of palliative care and what aspects of it have prompted the above improved clinical outcomes. Such questions are addressed in part from the standpoint of smoking cessation in patients with incurable metastatic cancer.

What is palliative care?

But what is palliative care? Surprisingly, many healthcare providers advocate for it, implement it, but fail to define it. For example, in the study referenced above, Temel and others described their palliative care intervention as described immediately below [2]:

"General guidelines for the palliative care visits in the ambulatory setting were adapted from the National Consensus Project for Quality Palliative Care and were included in the study protocol. Using a template in the electronic medical record, palliative care clinicians documented the care they provided according to these guidelines. Specific attention was paid to assessing physical and psychosocial symptoms, establishing goals of care, assisting with decision-making regarding treatment, and coordinating care on the basis of the individual needs of the patient."

Moreover, these investigators allude to a broad spectrum of tasks, including educating patients about illness, working to mitigate symptoms, helping patients with decision-making, helping patients cope with a life-threatening illness, and providing direction for engaging other healthcare providers as members of the team—all of which detract from our ability to know what drives the benefits of a palliative care consultation and what drives these improvements in quality of life and presumably survival. This multidimensional aspect of palliative care also underscores the need to prioritize the needs of patients over time.

Smoking as a case-in-point: should smoking cessation be a priority for patients with early-stage lung cancer? Yes

Smoking cessation in patients with early-stage lung cancer is a well-defined priority. Early-stage disease patients who continue to smoke suffer an early demise either from smoking-induced infections or from the development of second malignancies; patients who continue to smoke double their risk of dying from one of the causes cited above compared to those who stop. These findings have been demonstrated prospectively in a study from Barrera and others, who showed that current smokers suffer a 23% risk of postoperative complications

compared to non-smokers who had only an 8% risk; slight degradations in complication rates occurred over time based on when smoking cessation occurred with respect to surgery [3]. A similar message was generated from a reanalysis of the National Lung Cancer Screening Trial, which showed that ongoing smokers had a lung cancer–specific hazard ratio of 2.14–2.29 and an all-cause mortality hazard ratio of 1.79–1.85 [4]. In contrast, former smokers who had not smoked for 7 years manifested a 20% reduction in mortality. Under such circumstances—that is, after a diagnosis of early-stage lung cancer—the justification for recommending smoking cessation is evident and strong.

The more challenging question: should smoking cessation be a priority for patients with metastatic lung cancer?

Although some organizations endorse smoking cessation efforts with such statements as, "If you or your loved one has been diagnosed with cancer, quitting tobacco use is one of the best goals a person can have to improve the chances of successful cancer treatment," it remains unclear whether similar benefits occur in patients with incurable metastatic non-small cell lung cancer as they do for patients with a curable cancer [5, 6]. It remains unclear whether this same message to stop smoking should prevail among patients with metastatic disease.

The data to justify smoking cessation in the setting of metastatic incurable cancer are sparse. In one of the few studies to examine this issue, Lennes and others retrospectively reviewed the medical records of 68 deceased patients and examined whether patients had received counseling for smoking cessation by the second clinic visit [7]. These investigators found that 10 patients were smokers and that half had received counseling for smoking cessation. In multivariate analyses, it appears that patients who had received counseling lived long than those who did not with the reported differences in survival as follows: 7.2 months versus 4.3 months; hazard ratio 0.33, $p = 0.009$. Obvious limitations of this study include its small sample size and retrospective study design. Yes, these data—coupled with the fact that smoking cessation might provide immediate benefit to patients with improved oxygenation, lowering of blood pressure, improvements in smell, improvements in taste, better circulation and better breathing, less fatigue, and better cognition—lead to the provocative conclusion that speaks in favor of smoking cessation among patients with metastatic non-small cell lung cancer.

In contrast, three avenues of thought might lead healthcare providers to question whether smoking cessation should be a high priority palliative intervention in patients with metastatic non-small cell lung cancer.

First, minimal survival benefit to smoking cessation in patients with metastatic non-small cell lung cancer

In larger studies that have examined the survival benefits of smoking cessation in patients with metastatic non-small cell lung cancer, those benefits seem modest. In understanding these smoking-related outcomes, it is important to focus on patients who have stopped smoking—as opposed

to patients who have never smoked—and to compare outcomes between former and current smokers. This distinction between former smokers and never smokers is important because focusing on the former creates a situation more akin to what potentially occurs when patients are asked to stop smoking and because the exclusion of never smokers side-steps the better outcomes sometimes seen in never smokers who developed lung cancer patients and who appear to have a biologically distinct, more favorable malignancy. Interestingly, it is near impossible to be able to focus on former and current smokers, as most studies do not make comparisons between these groups; never smokers tend to get included in the mix of former smokers.

Only a few studies have tried to focus on former and current smokers. In a prospective observational study, Li and others examined 1214 patients with advanced non-small cell lung cancer [8]. In multivariate analyses, these investigators found that none of their smoking variables influenced survival. They reported a hazard ratio of 0.955 (95% confidence intervals 0.572, 1.596) for patients who continued to smoke during cancer therapy (referent group was comprised of never smokers) ($p = 0.86$). In contrast, in a 2471 patient study, Kogure and others observed that, compared to non-smokers, current smokers manifested a higher risk of death compared to non-smokers, but findings were not consistent across tumor histologies [9]. Interestingly, with an adenocarcinoma histology, the hazard ratio was 1.3 (95% confidence intervals 1.2, 1.5; $p < 0.001$), but with a non-adenocarcinoma histology, the hazard ratio changed to 0.99 (95% confidence intervals 0.75, 1.31; p value not reported). As alluded to earlier, these contrasting findings may reflect inherently better outcomes among never smokers who develop lung cancer and not necessarily a favorable outcome based on smoking cessation. Other studies of smaller size have shown at best only modest benefits related to smoking cessation and survival, although the ambiguity of smoking status—never smokers versus former smokers as opposed to current smokers versus former smokers—continues to confound the interpretation of these results.

Second, immunotherapy and its impact on the need for continued prioritization on the issue of smoking cessation

With new therapies—and specifically immunotherapy that includes check point blockade—the treatment for lung cancer has favorably evolved. Interestingly, some of these improvements appear to be biologically based and associated with smoking status. Such new developments might lead one to question how critically it is to advise patients with metastatic disease to stop smoking. More specifically, tobacco smoke generates DNA damage which in turn leads to mutations. These mutations alter the tumor's immune environment, potentially carrying therapeutic implications. It is well known that such mutations are critical to inducing favorable outcomes with immunotherapy such as checkpoint inhibitors. In fact, Desrichard and others recently expounded upon this scenario [10]. Focusing on 130 patients with squamous cell lung cancer, these investigators examined a gene expression data set and observed that a more aggressive smoking

history led to mutational signatures that were associated with higher levels of immune infiltration. These findings suggest that some smoking-induced cancers might be more responsive to checkpoint inhibitors.

Indeed, the above seems to be the case. Kim and others conducted a meta-analysis of six randomized controlled trials from 2389 ever smokers and 413 never smokers [11••]. Survival was a key outcome. Interestingly and in keeping with the implications in the paragraph immediately above, progression-free survival in a first-line treatment setting trended toward improvement among patients with a smoking history (HR = 0.85 [95% CI, 0.71–1.10], $p = 0.07$). Beyond first-line chemotherapy, immune checkpoint inhibitors prolonged overall survival with chemotherapy in patients with a smoking history (HR = 0.70 [95% CI, 0.63–0.79], $p < 0.00001$); of note, this finding was not observed in non-smokers. Although the authors describe smoking status as "a predictive marker" of efficacy of checkpoint inhibitors, one might wonder if a mechanistic basis for these observations might also be at play. Furthermore, these findings are all the more impactful in view of another meta-analysis, which reached similar conclusions [12]. Taken together, the findings from these meta-analyses raise the question of whether smoking cessation should be dropped to a lower level of prioritization when rendering palliative care to some patients with lung cancer, particularly in view of the fact that immunotherapy is now considered a first-line therapy in patients with metastatic non-small cell lung cancer.

Similarly, Norum and Nieder undertook a systematic review of the published literature [13•]. These authors described results from nine previous publications which focused on high programmed death ligand (PD-L1) expression of ≥ 50%. These authors described how, in three studies, such high expression correlated with a prior history of smoking, and they described how, in six studies, a higher tumor response rate occurred in smokers. For example, in the KEYNOTE-001 study, the median progression-free survival among patients with a smoking history was 4.2 months in contrast to 2.1 months among patients who never smoked. Overall survival was also more favorable, 14.3 and 8.8 months, respectively [14]. In keeping with the above line of thinking, these authors attributed these higher tumor response rates to a higher mutational burden that arose from a history of smoking.

In contrast to the above findings, KEYNOTE-024 provided data in favor of smoking cessation [15]. This study did in fact make the distinction between current and former smokers. Investigating pembrolizumab for the treatment of lung cancer, these investigators observed an overall tumor response rate of 45% among former smokers in contrast to 28% in current smokers. Similarly, the hazard ratio for progression-free survival was 0.68 and 0.47, respectively. These data speak in favor of smoking cessation in the setting of metastatic non-small cell lung cancer. These data also further illustrate the point that with improvements in survival, the previous nihilism associated with metastatic lung cancer is fading, a situation which suggests that smoking cessation might be a more worthwhile endeavor than previously thought. But the question still lingers: within the

context of a single study—albeit an important one—to support smoking cessation in the setting of metastatic disease, to what extent should we be advising patients to stop smoking?

Third, the challenge of smoking cessation for the individual patient

Smoking cessation is difficult. Of note, in a presumed effort to minimize the failure rates of smoking cessation, the Centers for Disease Control describes the success of such efforts from the standpoint of statistics that convey the "percentage of adult daily cigarette smokers who stopped smoking for more than 1 day" [16]. The foregoing was the case in only 55% of all adult smokers, 67% of smokers aged 18 through 24, 60% of smokers aged 25 through 44, 50% of smokers aged 45 through 64, and 47% of smokers aged 65 and older. With age, it becomes more difficult to quit, an observation that is particularly germane to lung cancer patients who tend to be older. The challenges of smoking cessation make one wonder whether efforts to stop smoking should be aggressively advised to patients after they have learned of an incurable diagnosis. These challenges are even further underscored by the abysmally low success rates of sustained abstinence observed in a recent trial from Halpern and others [17]. Admittedly, some patients may choose to try to stop smoking to feel in control of their health, but others, especially if they had experienced previous unsuccessful attempts, may become frustrated from further efforts to try. One cannot help but wonder whether this situation applies only to a minority of patients and whether smoking itself helps these patients cope with stress, especially after a diagnosis of metastatic lung cancer. Healthcare providers who are helping patients sort through palliative care options must consider the emotional consequences of advising smoking cessation in patients with an incurable cancer and with a large burden of innumerable other issues that stem from an incurable cancer diagnosis. Although one can never condone smoking, the question of prioritization remains unanswered.

Conclusion

The convergence of two rapidly evolving fields—the treatment of non-small cell lung cancer and palliative care—illustrates the need to continuously reassess and prioritize interventions relevant to the latter. Without question, patients with early-stage lung cancer should be advised to stop smoking. However, the decision to advise the same in patients with metastatic lung cancer is far less straightforward. Although recent data at times question the value of smoking cessation in patients with metastatic non-small cell lung cancer, particularly in the face of the widespread use of checkpoint inhibitors and although the psychological challenges of stopping smoking can be great for cancer patients, other findings—specifically the results of the KEYNOTE-024 trial—suggest the need to raise the question of smoking cessation in all patients. Perhaps, the best compromise is to rely on clinical judgment on

when, how, and if to discuss smoking cessation in patients with metastatic non-small cell lung cancer.

This review concludes with one other important point. Cancer treatment is changing at a rapid rate, as seen in the current, state-of-the-art treatment of non-small cell lung cancer. Other areas of cancer care are also changing quickly. The fact that cancer care and palliative are so intertwined is well illustrated in this issue of smoking cessation. Hence, our overarching concluding point is that, at the very least, it behooves palliative care providers to remain abreast of a broad scope of scientific developments not only in their field of palliative care but in other related fields, such as oncology. Changes in one of these fields might well impact the other and influence the prioritization of effort.

Compliance With Ethical Standards

Conflict of Interest

Konstantinos Leventakos, Anna J. Schwecke, Erin Deering, Elizabeth Cathcart-Rake, Anna C. Sanh, and Aminah Jatoi declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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