Editorial

Quality of life for non-small cell lung cancer patients in the age of immunotherapy

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Non-small cell lung cancer (NSCLC) is a very common and devastating disease that is accompanied by a range of symptoms. Patients can experience symptoms specific to their disease process (such as cough or dyspnea) or more generalized symptoms (such as fatigue and loss of appetite). Often times these can lead to or exacerbate psychological symptoms. In one study, depression was not only seen in a third of all lung cancer patients before the initiation of treatment, it also persisted in more than half of those patients (1). The investigators found that functional impairment is the most important risk factor for depression, and other independent factors that predicted depression include fatigue, symptom burden, and performance status (1). Therefore, it is unsurprising that maintaining quality of life (QOL), independence, and the ability to perform normal activities were ranked as the three most important issues among patients with lung cancer (2).

Given the incurable nature of metastatic NSCLC, the goals of therapy should not only focus on attempts at controlling the disease, but it should also be directed at optimizing the patient's QOL. A 2010 study by Temel *et al.* demonstrated that the introduction of palliative care shortly after diagnosis improved both QOL and mood (3). In addition, the patients that received early palliative care also had less aggressive care at the end of life and longer survival (3). Other means to improve QOL include palliative radiation for the treatment of intrathoracic disease and symptomatic metastases. For example, palliative radiotherapy by means of endobronchial brachytherapy can be utilized in attempt to alleviate symptoms of dyspnea, cough, hemoptysis, and obstructive pneumonia. In addition, whole brain radiation is a noninvasive form of palliative radiotherapy that is often employed with the goal of improving QOL for NSCLC patients with brain metastases. While palliative radiotherapy can be an effective means to relieve symptoms, it does require daily treatment visits that could lead to significant time and financial burdens on both the patients and their families.

Chemotherapy in general has been shown to improve QOL when compared to best supportive care, likely due to better overall physical functioning and alleviation of disease-related symptoms (4). Due to the differences in the toxicity profiles of various chemotherapeutic agents, platinum containing regimens have demonstrated superiority in efficacy, toxicity, and QOL among traditional chemotherapy (4). However, the administration of subsequent lines of chemotherapy after progression of disease has been associated with worse outcomes with regards to physical conditioning and symptom burden (5). Despite efforts to maximize QOL, patients unfortunately may suffer a significant amount of therapy-related adverse effects as a consequence of their treatment regimen. In addition, when Silvestri *et al.* looked at patients' willingness to undergo cytotoxic chemotherapy, he found that patients with a significant degree of symptoms will prioritize symptom relief over survival (6). Thus, the ideal choice in palliative

systemic therapy should carry a very limited side effect profile.

More recently, immune checkpoint inhibitors have demonstrated success in the treatment of NSCLC patients who have failed traditional therapies and are now finding a role in first line treatment as well (online: http://tlcr.amegroups.com/public/system/tlcr/supp-tlcr-18-80-table.pdf) (7-15). Nivolumab, pembrolizumab, and atezolizumab are three immune checkpoint inhibitors that are currently approved for the second line treatment of advanced NSCLC based on a number of studies (7,9-12,14). In addition, pembrolizumab received indication for first line treatment for those patients who have high PD-L1 expression or in combination with carboplatin and pemetrexed based on the KEYNOTE-024 and KEYNOTE-021 trials (15,16).

The superiority of nivolumab, pembrolizumab and atezolizumab over docetaxel in the second line setting in terms of response rate (RR), overall survival (OS) and progression-free survival (PFS) has been shown in multiple studies (7,9-12,14-16). With regards to safety, the CheckMate 017, CheckMate 026, CheckMate 057 trials have consistently shown favorable outcomes for nivolumab, when compared to docetaxel or platinum doublet therapy (7,9,10). Both the OAK and POPLAR trials demonstrate the safety superiority of atezolizumab over docetaxel (11,12). Additionally, KEYNOTE-010, KEYNOTE-021, KEYNOTE-024 trials also display a good trend in the safety profile for pembrolizumab, compared with docetaxel and platinum based chemotherapy (14-16). The incidences of grade 3 and higher adverse events with immunotherapy compared to chemotherapy are 7–18% for nivolumab (*vs.* 51–57% for docetaxel) (7,9,10), 13–39% for pembrolizumab (*vs.* 39–53% for chemotherapy) (14-16), and 11–15% for atezolizumab (*vs.* 39–45% for docetaxel) (11,12), deeming immune checkpoint inhibitors to be safer than chemotherapy. Only one study reported greater adverse reactions among those receiving immunotherapy; however, this group had longer treatment times (1.6× longer) which may account for the increase in unfavorable events (15).

With this data in mind, it is commonly assumed that lower frequency of grade 3 or higher adverse events equates to a better overall QOL. Although this is a logical assumption, it is not always substantiated. Few studies have specifically examined patient-reported QOL scores. Given that patients with advanced NSCLC have symptoms that can negatively impact functioning; health related (HR) QOL scores need to be assessed together with survival data.

Patient reported outcomes (PROs) has been assessed in CheckMate 017, KEYNOTE-024 and OAK trials using a variety of QOL measures: the Lung Cancer Symptom Scale (LCSS), European Quality of Life Five Dimensions (EQ-5D) questionnaires, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core 30 items (C30) and Lung Cancer 13 items (LC13). The QLQ-C30 assesses five functional measurements (physical, responsibility, emotional, thought, and social), three symptom scales (pain, fatigue, nausea), and a number of single items assessing commonly experienced symptoms in the cancer setting (dyspnea, insomnia, anorexia, altered bowel habits) (17). The QLQ-LC13 is a supplementary questionnaire to be used in conjunction with the QLQ-C30; however, the QLQ-LC13 and LCSS exclusively focuses on symptoms associated with lung cancer (such as dyspnea, cough and hemoptysis) and its treatment (dysphagia, alopecia, and peripheral neuropathy) (18). Lastly, the EQ-5D is not a cancer specific tool, but rather a means to measure general health through five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) (19).

Brahmer *et al.* assessed PROs from the KEYNOTE-024 examining change from baseline to week 15 in QLQ-C30 GHS/QOL tally and time to deterioration of symptoms (specifically, cough, chest pain, and dyspnea) in the QLQ-LC13 (20). Overall, patients who received pembrolizumab reported improved QOL compared to chemotherapy. Those in the pembrolizumab group reported significantly improved QOL measures at 15 weeks, compared to a decline in QOL in the chemotherapy group (improvement of 6.9 points *vs.* a decline of 0.9 points, P=0.002). As previously mentioned, patients reported optimal QOL scores with platinum-based chemotherapy over other types of chemotherapy and palliative care; however, by demonstrating superior QOL ratings over platinum-based chemotherapy, the current findings lend support to the idea that immunotherapy may be the optimal treatment choice to preserve QOL in patients with NSCLC.

This report also demonstrated that fewer pembrolizumab treated patients reported deterioration, compared to those who underwent chemotherapy (31% *vs.* 39%) (20). Moreover, the time to deterioration was longer in those treated with pembrolizumab then chemotherapy (P=0.029). Additionally, although disease progression was found to have a negative effect on QOL regardless of treatment group, pembrolizumab led to a smaller decline in QOL in those with progression, when compared to the chemotherapy group (20). Progression of disease commonly leads to an

increase in symptomatic burden and consequently the decline in QOL and psychological well-being. Therefore, preserving and improving QOL measures is of the utmost importance at time of progression. The authors noted promising findings; pembrolizumab may improve QOL irrespective of disease state (20).

Furthermore, this study brings light to the fact that the instruments used to assess QOL may not be appropriate for evaluation in immunotherapy, as they were developed for QOL assessment in chemotherapy (20). Albeit addressed as a limitation of the paper, this point calls for further focus in the realm of QOL research. As we are currently experiencing a boom in the use and application of immunotherapies, a questionnaire developed specifically to capture immunotherapy-associated adverse effects (such as pneumonitis, pruritus and pancreatitis) is needed.

Overall, the QOL results from KEYNOTE-024 are encouraging. Equivalent trends were also shown with atezolizumab. PROs were collected from participants in the OAK trial using EORTC QLQ-C30 and QLQ LC13 to demonstrate clinical benefit of treatment regimen. Time to deterioration in physical and role function was delayed among those who received atezolizumab, when compared to chemotherapy. Atezolizumab led to a decrease in clinically worsening symptoms, including diarrhea (P<0.0001), sore mouth (P<0.0001), dysphagia (P<0.0052), peripheral neuropathy (P<0.0001), and alopecia (P<0.0001) (13).

The results reported by Brahmer *et al.* [2017] were similar to that observed in the CheckMate 017. In the CheckMate 017 trial, HRQOL was examined by using the LCSS and EQ-5D questionnaire at baseline and various time points until deterioration. At week 12, nivolumab LCSS average symptom burden index (ASBI) scores were similar to that of docetaxel (20.0% *vs.* 21.9%); however, at weeks 16–54 and 42–84 those who received nivolumab reported significant improvement and clinically meaningful improvement in ASBI scores, respectively. At week 36, a clinically meaningful deterioration was observed with docetaxel. Particularly noteworthy, the mean EQ-5D index of the nivolumab group exceeded those of the general American population in the later weeks, which may indicate the return of baseline health status with sustained treatment (8).

Taken together, these studies lend support for the clinical and tolerability benefits associated with the use of immune checkpoint inhibitors compared to docetaxel or platinum based chemotherapy. In addition to the established RR, PRS and OS benefit seen in nivolumab, atezolizumab and pembrolizumab, the use of immunotherapy may maintain or improve HRQOL among patients with NSCLC.

Given the importance of QOL to patients with advanced NSCLC, there must be a balance between improving survival and optimizing the patient's QOL by reducing both disease related symptoms and therapy related side effects. The recent development of immune checkpoint inhibitors provides treatment options that are able to offer increased survival while reducing therapy related toxicities when compared to traditional cytotoxic chemotherapy. As cancer therapy becomes more precise and targeted, patients will hopefully benefit from better responses to treatment without having to suffer from associated adverse effects.

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Footnote

Conflicts of Interest: Dr. RA Ramirez serves as a speaker for Guardant Health, Merck & Co., Inc., Genentech, Inc., AstraZeneca, and Ipsen Biopharmaceuticals, Inc. He is also a consultant for Biotheranostics, Advanced Accelerator Applications, and Novartis Pharmaceuticals, Corp. The other authors have no conflicts of interest to declare.

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