Treatment sequences of patients surviving at least two years after initiation of nivolumab in previously treated advanced non-small cell lung cancer (aNSCLC): contribution of time-kerning analysis

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Introduction

- More than 46,000 people were diagnosed with lung cancer in France in 2018.1
- Lung cancer is frequently diagnosed at an advanced stage, with 5-year survival rates historically not exceeding 5%.2 Non-small cell lung cancer (NSCLC) is the most common histological subtype, accounting for 80% of all cases. In phase III clinical trials, immunotherapies (PD-1/PD-L1 inhibitors) in combination with nivolumab, pembrolizumab and atezolizumab showed greater efficacy compared to docetaxel in second-line treatment of advanced NSCLC.3
- Nivolumab has been available in France since January 2015, at first under the Temporary Autorisation for Use programme (ATU), and then as a marketed drug for locally advanced or metastatic NSCLC patients previously treated with chemotherapy.4

UNIVOC background

UNIVOC is a cohort of 10,412 patients including all patients with aNSCLC who had started treatment with nivolumab within two years of its availability in France, identified through the hospital databases Programme de Médicalisation des Systèmes d’Information, PMSI). The UNIVOC study previously described the outcomes of subsequent retreatment and rechallenge with a PD-1 inhibitor after nivolumab discontinuation5. The long-term survival of patients treated with immunotherapy including pembrolizumab.6

Methods

Study rationale

- Long-term management (2 years of treatment initiation) of patients with aNSCLC treated by nivolumab is poorly documented.
- Treatment sequences analyses are usually pre-defined, simplistic and not time-dependent.
- Post-immunotherapy data in real-world clinical practice are limited and the heterogeneity of practices makes the analysis of treatment sequences complex. Thus, machine learning and innovative analytical approaches are relevant.

Study objectives

- To describe treatment sequences.
- To identify clusters of patients presenting similar treatment sequences.
- To determine patients’ profile from each cluster.

Results

TAK re_evaluated treatment sequences allowed to flag 4 different clusters within the population of 2,129 patients still alive 2 years after nivolumab treatment (Figure 6).

- Cluster 1 patients with nivolumab as the main treatment over the first 24 months, received almost continuously with a cumulative median duration (CMD) of 21.9 months. Grey/orange spots indicate retreatment/rechallenge with nivolumab.
- Cluster 2 patients with nivolumab as the main treatment (CMD: 16.5 months) followed by a short chemotherapy (CMD: 2.5 months) and/or a therapeutic break (CMD: 5.3 months).
- Cluster 3 patients with short nivolumab treatment (CMD: 6.4 months) followed by a long therapeutic break (CMD: 14.4 months) with or without chemotherapy.
- Cluster 4 patients with short nivolumab treatment (CMD: 5.3 months) followed by one or several lines of chemotherapy (CMD: 9.5 months).

After comparison of cluster 1 with all other ones, no association with hospital type, histology, or comorbidities could be identified. However, cluster 1 population was associated with younger patients (<60 years old) with recent lung cancer history (<1 year). Patients also had more brain metastases (except vs cluster 2) and more history of radiotherapy.

Finally, fewer patients had been treated with surgery since the beginning of their cancer care.

Analyses

- The analyses used machine learning techniques (Figure 2).
- The clustering technique was the Time sequence Analysis through K-clustering (TAK). It allowed us to model each patient’s pathway as a vector and search for common sequences and clustering of similar trajectories (Figure 3). Thus, TAK offered one image with all the features.
- Clinical characteristics of patients within the different clusters were analyzed. Characteristics such as age, gender, histology, previous treatment (radiotherapy, surgery), and hospital type were analyzed via a pairwise multinomial logistic regression.
- Therapeutic options were: immunotherapies (including nivolumab and pembrolizumab), chemotherapy anti-VEGF therapy (including pembrolizumab, bevacizumab and others) and treatment-free interval. For each cluster, cumulative median durations (CMD) of therapeutic options were calculated, and patients characteristics were described (sociodemographic, previous therapeutic management care and comorbidities).

Conclusion

Using a large sample of NSCLC patients still alive 2 years after nivolumab initiation, the Machine Learning approach enabled us classifying patients with similar treatment sequences and to identify 4 clusters of patients with distinct care features who as long-term survivors:

- Received nivolumab almost continuously (Cluster 1);
- Received nivolumab for a long time but discontinuous nivolumab treatment (Cluster 2);
- Discontinued nivolumab early and had no subsequent systemic treatment (Cluster 3);
- Discontinued nivolumab early and then started a subsequent chemotherapy (Cluster 4).

Patients in Cluster 1 appeared to be particularly different from other clusters. An in-depth study of their clinical profile could provide a better understanding of their specificities.

References


Disclosure

No conflicts of interest. All the authors contributed and approved this manuscript.

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