Predictive ability of a drug-based score in patients with advanced non–small-cell lung cancer receiving first-line immunotherapy

Running title: A predictive drug score for first-immunotherapy in NSCLC.

Predictive ability of a drug-based score in advanced non-small cell lung cancer patients receiving first-line immunotherapy.

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Abstract

Background: We previously demonstrated the cumulative poor prognostic role of concomitant medications, on the clinical outcome of advanced cancer patients treated with immune checkpoint inhibitors, creating and validating a drug-based prognostic score to be calculated before immunotherapy initiation in patients with advanced solid tumors. This "drug score" was calculated assigning score 1 for each between PPIs and antibiotics administration until a month before cancer therapy initiation, and score 2 in case of corticosteroids intake. Good risk group included patients with score 0, intermediate risk with score 1-2 and poor risk with score 3-4

Methods: Aiming at validating the prognostic and putative predictive ability depending on the anticancer therapy, we performed the present comparative analysis in two cohorts of advanced non-small cell lung cancer (NSCLC) respectively receiving first-line pembrolizumab or chemotherapy through a random case-control matching and through a pooled multivariable analysis including the interaction between the computed score and the therapeutic modality (pembrolizumab vs chemotherapy).

Results: 950 and 595 patients were included in the pembrolizumab and chemotherapy cohorts, respectively. After the case-control random matching, 589 patients from the pembrolizumab and 589 chemotherapy cohorts were paired, with no statistically significant differences between the characteristics of the matched subjects. Among the pembrolizumab treated group, good, intermediate and poor risk evaluable patients achieved an ORR of 50.0%, 37.7% and 23.4%, respectively ($p < 0.0001$) while among the chemotherapy treated group of 37.0 %, 40.0% and 32.4%, respectively ($p = 0.4346$). The median PFS of good, intermediate and poor risk groups was 13.9 months, 6.3 months and 2.8 months, respectively within the pembrolizumab cohort ($p < 0.0001$), and 6.2 months, 6.2 months and 4.3 months, respectively within the chemotherapy cohort ($p = 0.0280$). Among the pembrolizumab treated patients the median OS for good, intermediate and poor risk patients was 31.4 months, 14.5 months and 5.8 months, respectively ($p < 0.0001$), while among the chemotherapy treated patients was 18.3 months, 16.8 months and 10.6 months, respectively ($p = 0.0003$). A similar trend was reported considering the two entire populations. At the pooled analysis, the interaction term between the score and the therapeutic modality was statistically significant with respect to ORR ($p = 0.0052$), PFS ($p = 0.0003$) and OS ($p < 0.0001$), confirming the significantly different effect of the score within the two cohort.

Conclusion: Our "drug score" showed a predictive ability with respect to ORR in the immunotherapy cohort only, suggesting it might be a useful tool for identifying patients unlikely to benefit from first-line single agent pembrolizumab. Additionally, the prognostic stratification in terms of PFS and OS was significantly more pronounced among the pembrolizumab treated patients.

Keywords: predictive score; concomitant medications; pembrolizumab; immunotherapy; non-small cell lung cancer; first-line.

Introduction

In recent years, the impact of patient-related variables on anticancer treatments' efficacy has been widely explored, especially in the field of immune checkpoint blockade. Several works evaluated the prognostic and predictive value of key baseline factors in population of patients receiving immunotherapy [1-6]. In a previous publication, we demonstrated the cumulative poor prognostic role of concomitant medications, namely corticosteroids, antibiotics and proton-pump inhibitors (PPIs), on the clinical outcome of advanced cancer patients treated with immune checkpoint inhibitors (ICI) [7]. With this premise, we created and validated a drug-based prognostic score to be calculated before immunotherapy initiation in patients with advanced solid tumors. This "drug score" was calculated assigning score 1 for each between PPIs and antibiotics administration until a month before cancer therapy initiation, and score 2 in case of corticosteroids intake. Good risk group included patients with score 0, intermediate risk with score 1-2 and poor risk with score 3-4 (**Table 1**). Our findings of a shorter progression free survival (PFS, $p < 0.0001$) and lower objective response rate (ORR, $p = 0.0297$), besides of a shorter overall survival (OS, $p < 0.0001$), for patients with the higher score, found in the training cohort and confirmed in a large validation cohort, suggested a possible predictive role of the model in this patient population [7].

To verify this hypothesis, and to test the prognostic and putative predictive ability depending on the anticancer therapy, we planned the present comparative analysis in two cohorts of patients with advanced non-small cell lung cancer (NSCLC) respectively receiving pembrolizumab or chemotherapy as first-line treatment.

Materials and Methods

The aim of this analysis was to investigate the impact of our "drug score", based on three classes of key baseline concomitant medications, in a cohort of metastatic NSCLC patients (tumor PD-L1 expression $\geq 50\%$) treated with first-line pembrolizumab, and in a cohort of NSCLC patients (*EGFR*-wild type) receiving standard chemotherapy as first-line approach, respectively, finally evaluating the true predictive effect of the model.

Overall, 31 Institutions retrospectively included patients treated from January 2017 to May 2020 (pembrolizumab cohort) and from January 2013 to May 2020 (chemotherapy cohort). The two NSCLC patient series were described in prior publications [6, 8-9]. The endpoints were ORR, PFS and OS. Methods regarding clinical outcomes estimation were previously detailed [6, 8-9]. Data cut-off period was September 2020 for the present analysis. Concomitant medications at

the first-line treatment commencement were collected from patient clinical records, within 30 days before first-line treatment initiation.

To compare the score performance between the two cohorts, a random case-control matching was performed, randomly pairing cases and controls (extracted by the chemotherapy and pembrolizumab cohorts) basing on the drug score (**Table 1**), Eastern Cooperative Oncology Group – Performance Status (ECOG-PS, 0-1 *vs* 2), age (< 70 *vs* ≥ 70 years old), and gender (male *vs* female).

To further assess the potential different impact of the drug score between the two cohorts, we also performed a pooled analysis of the two entire populations, using a multivariablee regression model (including the drug score as a continuous variable), including the interaction term between the computed score and the first-line treatment modality, used as a covariate (pembrolizumab *vs* chemotherapy). The key covariates were age (< 70 *vs* ≥ 70), sex (male *vs* female), ECOG-PS (0-1 *vs* ≥ 2), smoking status (current/former *vs* never smokers), central nervous system metastases (yes *vs* no), bone metastases (yes *vs* no) and liver metastases (yes *vs* no).

Statistical analyses were performed using MedCalc Statistical Software version 18.11.3. Median PFS and OS were evaluated by Kaplan-Meier method and log-rank test was used for univariablee analyses. Median follow-up was calculated according to reverse Kaplan-Meier method. Chi-square test was used for the univariable analysis of ORR. Logistic regression and Cox proportional hazards regression were used for OS and PFS for the fixed multivariable analyses. Alpha level for all analyses was set to $p < 0.05$. Adjusted hazard ratios (HRs) and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Considering that all the selected variables were categorical, a caliper width of < 1 for the standard deviation was used for the random case-control matching. The concordance index (C-index) according to the computed score was also computed for each cohort.

Results

Respectively, 950 patients and 595 patients were included in the pembrolizumab and chemotherapy cohorts. Approximately half of the patients was elderly (≥ 70 years), most of them were male, current or former smokers and had a good ECOG PS. Baseline corticosteroids, systemic antibiotics and PPIs use was reported in about a quarter, one seventh and one half of the patients, respectively: the complete patient characteristics were reported in **Supplementary Table S1**.

In the chemotherapy cohort, 545 patients (91.6%) received platinum-based doublets, while 50 patients received single-agent chemotherapy (8.4%). Additionally, 307 patients (51.6%) received ICI in later treatment lines. The median follow-up was 21.8 months (95%CI: 20.5-37.3) for the pembrolizumab cohort and 39.3 months (95%CI: 33.1-86.7) for the chemotherapy cohort. Within the pembrolizumab cohort, 39.3%, 42.4% and 18.3% of patients were grouped as good, intermediate and poor risk, respectively according to the drug score, whilst within the chemotherapy cohort 36.6%, 38.0% and 25.4% of patients were grouped as good, intermediate and poor risk, respectively. After the case-control random matching, 589 patients from the pembrolizumab and 589 patients from the chemotherapy cohorts were paired, with no statistically significant differences between the characteristics of the matched subjects. Table 2 detailed the outcomes analysis across the two matched cohorts. Among the pembrolizumab treated group, good, intermediate and poor risk evaluable patients achieved an ORR of 50.0%, 37.7% and 23.4%, respectively ($p < 0.0001$) (**Figure 1A**), while among the chemotherapy treated group of 37.0 %, 40.0% and 32.4%, respectively ($p = 0.4346$) (**Figure 1B**). The median PFS of good, intermediate and poor risk groups was 13.9 months, 6.3 months and 2.8 months, respectively within the pembrolizumab cohort ($p < 0.0001$) (**Figure 1C**), and 6.2 months, 6.2 months and 4.3 months, respectively within the chemotherapy cohort ($p = 0.0280$) (**Figure 1D**). Among the pembrolizumab treated patients the median OS for good, intermediate and poor risk patients was 31.4 months, 14.5 months and 5.8 months, respectively ($p < 0.0001$) (**Figure 1E**), while among the chemotherapy treated patients was 18.3 months, 16.8 months and 10.6 months, respectively ($p = 0.0003$) (**Figure 1F**). A score calculator is available as a web-app at: https://medscore.shinyapps.io/NSCCdrugbased_score/

A similar trend was reported considering the two entire populations (**Supplementary Table S2**). The drug score was significantly associated with the ORR within the pembrolizumab cohort ($p < 0.0001$), but not in the chemotherapy cohort ($p = 0.4311$), while it was significantly related to PFS ($p < 0.0001$ and $p = 0.0120$, respectively) and OS ($p < 0.0001$ and $p = 0.0001$, respectively) in both the pembrolizumab and chemotherapy cohorts. The clinical outcomes analysis of the two entire populations is also reported in **Supplementary Figure S1**. In the pooled multivariable analysis (summarized in **Table 3**), the interaction between the score and the therapeutic modality was statistically significant with respect to ORR ($p = 0.0052$), PFS ($p = 0.0003$) and OS ($p < 0.0001$), confirming its significantly different effect between the two cohorts.

Discussion

The results of the present analysis clearly showed the prognostic value of our "drug score" in advanced NSCLC patients undergoing first-line chemotherapy and pembrolizumab immunotherapy. Nevertheless, the significant stratification with respect to ORR within the pembrolizumab cohort only, confirmed its predictive role selecting patients to be treated with first-line immunotherapy. Moreover, the concordantly significant interaction at the pooled analysis, revealed that even the prognostic layering is more pronounced for pembrolizumab treated patients compared with the chemotherapy treated group (**Table 3**), as intuitively suggested by the Kaplan-Meier survival curves.

Our findings suggest that in NSCLC patients baseline medications are more likely to affect ICI's efficacy rather than the cytotoxic mechanism of action of chemotherapy. From this perspective, it is correct to assume that a putative immune-modulatory effect of concomitant medication would have affected clinical outcomes even in patients receiving chemotherapy [10-11]. Additionally, corticosteroids, PPI and antibiotics (to a lesser extent), are known to be associated to adverse baseline features, including worse performance status and higher burden of disease [12-13], therefore they could retain their negative role regardless of the cancer-oriented treatment. However, the stratification ability of the "drug score" is significantly different between the two cohorts, with a greater magnitude within the pembrolizumab cohort.

Interestingly, considering the prognostic ability of this score across the cohorts, we are allowed to assume that it would significantly stratify even NSCLC patients receiving first-line chemo-immunotherapy combinations. Considering the current debate about the best first-line treatment option (between single-agent immunotherapy and combinational approaches) for NSCLC patients with a high PD-L1 tumor expression [14], a further tool to categorize patients would be useful in that setting and the hypothesis is worth of additional investigations.

The present score is the first that simultaneously assess the impact of three different medications widely used in advanced cancer patients. Intriguingly, all these three drugs have the potential to modifying the host microbiota and we interpreted these findings as epiphenomenon of a patient-oriented modulation of the antitumor immune response [7]. Several evidence have already suggested that the systemic inflammation may affect immunotherapy efficacy in cancer patients [15]. Such inflammatory status might be measured through some blood parameters, including neutrophil and platelets blood counts, serum lactate dehydrogenase, albuminemia, neutrophil to lymphocyte ratio (NLR), derived neutrophils / (leukocytes minus neutrophils) ratio (dNLR), and blood cholesterol. These parameters have been evaluated alone and combined in prognostic models [5,16]. Similarly, we can assume that some drugs, which were confirmed to have microbiota modifying effects [17], may affect this inflammatory status, finally affecting immunotherapy efficacy. Considering that standpoint, the more relevant difference between the abovementioned parameters and the drugs included in our score, is that we can control their

intake, modulating their administration according to the perspective of starting a first-line immunotherapy, although not for every patient (e.g. when the need of a palliative treatment outweighs the expected benefit of immunotherapy).

We must acknowledge several limitations to the present analysis. The retrospective nature (possible missing clinical and drug history data) and the lack of centralized imaging review, the different median follow-up period between the two cohorts, and the data lack availability regarding PD-L1 tumor expression among the chemotherapy treated patients.

Conclusion

In terms of PFS and OS, our "drug score" showed a significant prognostic ability in NSCLC patients either receiving first-line immunotherapy or chemotherapy, however the stratification was significantly more pronounced among the pembrolizumab treated group. Additionally, the score showed a predictive role with respect to ORR within the immunotherapy cohort only, suggesting that it might be a useful tool for identifying patients unlikely to benefit from first-line single agent pembrolizumab. Concomitant therapies could be considered a modifiable factor prior immunotherapy commencement, therefore baseline medications should be always carefully checked, recommending patients to keep only the truly unavoidable ones or delaying (if clinically feasible) the immunotherapy start after stopping one or more of these drugs. The accurate baseline assessment of this "drug score" should be explored in future prospective clinical trials and could also be used to stratify patients in randomized trials.

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Ethics approval and consent to participate

All patients provided written, informed consent to treatment with immunotherapy. The procedures followed were in accordance with the precepts of Good Clinical Practice and the declaration of Helsinki. The study was approved by the respective local ethical committees on human experimentation of each institution, after previous approval by the coordinating center (Comitato Etico per le provice di L'Aquila e Teramo, verbale N.15 del 28 Novembre 2019).

Authors' contributions

All authors contributed to the publication according to the ICMJE guidelines for the authorship (study conception and design, acquisition of data, analysis, and interpretation of data, drafting of manuscript, critical revision). All authors read and approved the submitted version of the

manuscript (and any substantially modified version that involves the author's contribution to the study). Each author has agreed both to be personally accountable for his own contribution and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Figures legends

Figure 1. Clinical outcomes analysis according to the drug score in the matched populations. Objective response rate (ORR): **(A)** pembrolizumab cohort, **(B)** chemotherapy cohort. Progression Free Survival (PFS): **(C)** pembrolizumab cohort, **(D)** chemotherapy cohort. Overall Survival (OS): **(E)** pembrolizumab cohort, **(F)** chemotherapy cohort.

Supplementary Figure 1: Clinical outcomes analysis according to the drug score in the entire populations. Objective response rate (ORR): **(A)** pembrolizumab cohort, **(B)** chemotherapy cohort. Progression Free Survival (PFS): **(C)** pembrolizumab cohort, **(D)** chemotherapy cohort. Overall Survival (OS): **(E)** pembrolizumab cohort, **(F)** chemotherapy cohort.