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THE PROGNOSTIC ROLE OF HIGH BLOOD CHOLESTEROL IN ADVANCED CANCER PATIENTS TREATED WITH IMMUNE CHECKPOINTS INHIBITORS

Abstract

Immune-checkpoints inhibitors (ICI) have improved survival in numerous types of cancer. However, a great number of unselected patients still do not respond to ICI. Moreover, there is a need to identify biomarkers that could predict the prognosis of immunotherapy treated patients.

The aim of our study is to evaluate the prognostic value of baseline plasmatic cholesterol level in metastatic cancer patients treated with immunotherapy.

We retrospectively enrolled advanced cancer patients consecutively treated with ICI at our center between October 2013 and October 2018, in order to correlate the blood cholesterol level before treatment with overall survival (OS primary endpoint). The secondary endpoints were the correlation between baseline cholesterol and progression-free-survival (PFS), objective response rate (ORR) and toxicity (irAEs).

Among 187 patients with availability of baseline plasmatic cholesterol, 58 had cholesterol level > 200 mg/dl. The median age was 70 years. Primary tumors were: NSCLC (70.0%), melanoma (15.0%), renal cell carcinoma (9.1%), urothelial cancer (4.6%), head-neck carcinoma (0.9%), others (0.4%). The median follow-u*p* was 21.3 months. Both OS and PFS were better in patients with high plasmatic cholesterol level: median OS was 19.4 vs 5.5 months ($p = 0.001$) and median PFS was 6.1 vs 2.4 months ($p = 0.002$). The multivariate analysis confirmed the prognostic role of hypercholesterolemia in terms of OS but not PFS.

Hypercholesterolemia was associated to better outcomes in ICI treated cancer patients and, as expression of low-grade inflammation state, it could identify tumors more likely to be responsive to immunotherapy.

Key words: cholesterol, prognostic, biomarker, immune checkpoint inhibitor, cancer

Introduction

PD-1 (programmed cell death-1), PD-L1 (programmed cell death ligand-1) and CTLA-4 (cytotoxic T-lymphocyte antigen 4) are therapeutic targets for immune checkpoints inhibitors (ICIs). Anti-PD-1 antibodies, such as nivolumab and pembrolizumab, anti PD-L1 antibodies, like avelumab, atezolizumab and durvalumab, and even before anti CTLA- 4 antibodies, namely ipilimumab and tremelimumab, have been evaluated and approved as systemic treatments for various types of solid and hematological cancers [1-19]. Despite an improvement in terms of survival and response, a great number of unselected patients have still little or no benefit from immunotherapy [20]. Thus, identifying predictive or prognostic biomarkers for the ICI treated patient population is still an unmet need. With this aim, many studies have been carried out in the latest years. Up today, a number of biomarkers linked to the tumor have been prospectively and retrospectively evaluated, such as PD-L1 expression on immune cells or tumor cells, tumor mutational burden (TMB), diverse phenotypes of CD8+ tumor-infiltrating lymphocytes (TILs) and specific gene mutations [21]. On the other hand, a plethora of biomarkers linked to the host, such as neutrophil count, neutrophil-to-lymphocyte ratio (NLR), baseline serum lactate dehydrogenase (LDH) levels, C-reactive Protein (PCR) and the body mass index (BMI), have been also investigated by recent retrospective studies [22-26]. At present, none of the above-mentioned biomarkers are able to clearly identify patients more likely to benefit from immunotherapy, unless for isolate exception, as in the case of tumor PD-L1 expression levels in metastatic non-small-cell lung cancer (NSCLC) patients [14].

Recently, Cottrell and colleagues have found the cholesterol clefts in the histological specimens from NSCLC patients responders to neoadjuvant ICI immunotherapy. These are artifactual crystal-shaped spaces in tissue sections, indicating insoluble lipid accumulation and cell death [27].

As known, the metabolic syndrome is a chronic inflammatory condition characterized by a wide range of metabolic disorders, including obesity, hyperglycemia and dyslipidemia [28]. Despite being

historically recognized as a risk factor for cancer [29-31], recent studies have demonstrated the positive prognostic value of overweight in metastatic cancer patients treated with immunotherapy [25-26.]

The aim of our retrospective study was to investigate the potential prognostic role of baseline cholesterol levels among patients affected by metastatic cancer treated with ICIs.

Materials and methods

Patient eligibility

The present study included advanced cancer patients who consecutively underwent treatment with single agent anti-PD-1, anti-PD-L1 or anti-CTLA-4 or with the combination of anti-PD-1 and anti-CTLA-4, regardless of the treatment line, at the Medical Oncology Unit of the University-Hospital of Parma (Italy), from October 2013 to October 2018.

Patients were eligible if they had a histologically or cytologically confirmed diagnosis of locally advanced or metastatic NSCLC, melanoma, renal cell carcinoma (RCC), head and neck cancer, or urothelial carcinoma, and they must have been received at least one ICI administration. The availability of blood chemistry before starting immunotherapy was an inclusion criterion. Only patients with the availability of plasmatic cholesterol levels within six months prior to immunotherapy initiation were included in the present analysis. In the case of multiple baseline cholesterol values available for each patient, we considered the closest to the beginning of immunotherapy. All patients provided written informed consent to receive treatment with ICI. All the patients who were alive at the time of the data collection for the study provided an informed consent to be included in the analysis. The procedures followed were in accordance with the declaration of Helsinki. The study was approved by the local ethical committee.

Study design

We conducted a retrospective, monocenter study to investigate the prognostic value of baseline cholesterol in advanced cancer patients treated with ICIs.

The primary objective of our study was to evaluate the correlation between baseline plasmatic cholesterol and overall survival (OS, primary endpoint). The secondary objectives were the correlation between baseline plasmatic cholesterol and progression free survival (PFS), objective response rate (ORR), disease control rate (DCR) and toxicity (immune-related adverse events, irAEs), considered as secondary endpoints. In addition, with explorative aim, we investigated the possible impact of some pertinent drugs, such as statin, steroids and antibiotics, on OS and PFS.

OS was defined as the time from immunotherapy initiation until death from any cause. PFS was defined as the time from immunotherapy initiation to the first documented tumor progression or death. Patients not progressed/not died at the data cut-off of April 2019 were considered as censored at the time of the last follow-up. ORR was defined as the proportion of patients experiencing an objective response (either complete response or partial response) as best response to immunotherapy according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) [32]. DCR was defined as the percentage of patients achieving complete, partial response and stable disease. IrAEs were graded according to the Common Toxicity Criteria for Adverse Events (CTCAE; version 5.0) and cumulatively reported basing on the highest grade of occurrence of each respective type of irAE.

Basing on the primary tumor type, patients received ICIs as monotherapy with ipilimumab, nivolumab, pembrolizumab, avelumab, atezolizumab or durvalumab, or as combination therapy with ipilimumab and nivolumab, with standard doses and schedules.

We collected data from clinical records on medical history (i.e. metabolic disorders, hypercholesterolemia and hypertriglyceridemia), pharmacological history and plasmatic levels of total cholesterol, triglycerides and, if available, of low density lipoprotein (LDL) cholesterol and

high density lipoprotein (HDL) cholesterol, within six months prior to immunotherapy initiation, taking into account for the study purpose the closest assessment to the start of treatment.

The cut-off of 200 mg/dl and 150 mg/dl were used to define, respectively, hypercholesterolemia and hypertriglyceridemia, according to American Heart Association Guidelines [33].

The values of 50 mg/dl and 100 mg/dl (representing the mean values of the study population) were used as cut-off to define, respectively, high HDL cholesterol and high LDL cholesterol.

Univariate analyses were performed to assess the prognostic impact, in terms of OS and PFS, of cholesterol and other clinical parameters, namely ECOG PS, sex, BMI, smoke history, prior appendicectomy, high blood pressure, heart and hepatic comorbidities, renal failure, diabetes mellitus, hypercholesterolemia or hypertriglyceridemia, endocrine or autoimmune diseases, antibiotic or steroid therapy administered within 30 days before immunotherapy, statin therapy, primary tumor, metastatic sites (bone, liver, brain, lung, kidney, bladder, lymph-nodes, adrenal glands, skin, peritoneum or pleura, pancreatic or gastrointestinal lesions, pleural or peritoneal effusion), number of metastatic sites, number of previous lines of therapy and the respective best response, type of ICI administered and best response achieved, pseudo-progression, HBV and HCV serological markers, baseline plasmatic levels of total cholesterol, triglycerides, HDL and LDL cholesterol, N/L ratio < 3 vs ≥ 3 and N/L ratio < 4 vs ≥ 4, grade of immune-related adverse events (irAEs) experienced, administration of zoledronic acid or RANK-L inhibitors before, during or after immunotherapy in patients with bone metastases, and type of treatment administered after discontinuation of ICI. Median follow-up was calculated according to the reverse Kaplan-Meier method [34].

Patients and disease characteristics were described using rates (percentages), median values and ranges. Comparisons between cholesterol level groups (high vs low) were conducted using the χ^2 or Fishers's exact test (as appropriate) for categorical variables [35]. Distribution of OS and PFS were estimated using the Kaplan-Meier method [36]. Differences between cholesterol-level groups were examined with the log-rank test [37]. To explore if there is an association between OS and cholesterol

levels as continuous variables, we used Pearson's product-moment correlation (Pearson's r). Multivariable Cox proportional hazard models including the variables resulted as significant at the univariate analysis were used to estimate hazards ratios (HRs) for OS and PFS, and adjusted for primary tumor, line of therapy and statin therapy administration, regardless of their statistical significance at the univariate analysis 38. These covariates were included considering the heterogenous ICI treatments and some well-known prognostic factors.

SPSS Statistics 24.0 software (IBM Corporation, NY, USA) was used to carry out the statistical analyses. All statistical tests were two sided, and $p < 0.05$ was considered as statistically significant.

Results

Patients characteristics

Overall, 219 patients were screened, and 187 (85%) patients with available baseline cholesterol levels were enrolled in our study. At a median follow up of 21.3 months, 125 patients were died and 140 patients had experienced progression of disease.

The mean time from baseline cholesterol assessment to the beginning of immunotherapy was of 5.6 months. Patients baseline characteristics are summarized in Table 1. The median age of patients was 70 years. The majority were men (69.0%) and current or former smokers (57.2%). Primary tumors were: NSCLC (70.1%), melanoma (14.4%), renal cell carcinoma (9.6%), urothelial carcinoma (4.3%), head and neck cancer (1.1%), others (0.5%). 67 patients (35.8%) had ≤ 2 metastatic sites while 120 patients (64.1%) had more than 2 metastatic sites. The majority of patients received immunotherapy as second or more advanced lines (77.5%), while only 42 (22.5%) patients received immunotherapy as first line treatment. PD-1/PD-L1 inhibitors were the most frequently

administered agents: among these, 110 patients (58.8%) received nivolumab. Only two patients received a combination with ipilimumab and nivolumab.

Forty-three percent and 26.7% of patients experienced G1-2 or G3-4 irAEs during treatment with ICIs, respectively.

Fifty-eight out of 187 patients (31.0%) had a baseline level of plasmatic cholesterol higher than 200 mg/dl. Of them, 11 patients (18.9%) received statin therapy, 30 patients (52.6%) had medical history of hypercholesterolemia and 16 patients (27.5%) had medical history of hypertriglyceridemia.

The Pearson's r, to assess a possible association between OS and cholesterol levels as continuous variables, was 0.12 (one-sided $p = 0.05$).

Baseline cholesterol > 200 mg/dl was associated with absence of diabetes mellitus (OR: 0.33 [95%CI: 0.13-0.84], $p = 0.026$), no steroid therapy administration 30 days before the first cycle of ICI therapy (OR: 0.42 [95%CI: 0.21-0.86], $p = 0.025$), better disease control rate with ICI (OR: 2.65 [95%CI: 1.39-5.06], $p = 0.004$) and triglycerides < 150 mg/dl before the starting of immunotherapy (OR: 2.78 [95%CI: 1.43-5.41], $p = 0.004$).

On the other hand, high cholesterol did not correlate to ECOG PS, primary tumor, type of ICI, line of immunotherapy and statin administration.

Efficacy analyses

At the data cut-off of April 30, 2019, the median OS of the overall study population was of 7.8 months (95% CI: 5.1-10.5) (supplementary Figure 1). Patients with baseline plasmatic cholesterol > 200 mg/dl had significantly ($p = 0.001$) longer OS (19.4 months, 95%CI: 9.0-29.7) compared to that of patients with baseline cholesterol $\leq$ 200 mg/dl (5.5 months, 95% CI: 3.4-7.6), as shown in Figure 1. The other variables associated with prolonged OS at the univariate analyses were: ECOG PS = 0,

absence of hypertriglyceridemia in the medical history, no steroid nor antibiotic therapy within 30 days before the first ICI administration, number of metastatic sites ≤ 2, absence of liver or bone lesions, partial response or stable disease to the previous line of therapy, LDL cholesterol > 100 mg/dl and HDL cholesterol > 50 mg/dl and absence of pleural effusion and/or ascites. No statistically significant difference in OS was found for patients with BMI > 25 compared to those with BMI ≤ 25.

The multivariate analysis confirmed the positive prognostic role of hypercholesterolemia (HR: 0.48 (0.20-0.78), p = 0.003), together with that of ECOG PS = 0, complete/partial response or stable disease as best response to the previous line of therapy, absence of pleural effusion and/or ascites, and statin administration. All details of univariate and multivariate analysis are summarized in Table 2 and 3.

The median PFS of the overall study population was of 3.4 months (95% CI: 2.4 – 4.4) (Supplementary Figure 2). Patients with baseline plasmatic cholesterol > 200 mg/dl had significantly (p = 0.002) longer PFS (6.1 months, 95% CI 4.8-7.4) compared to that of patients with baseline cholesterol ≤ 200 mg/dl (2.4 months, 95% CI 1.5–3.2), as shown in figure 2. Landmark analyses for PFS at 6-months (65 patients included) and 12-months (34 patients included) did not show significant differences between high and low cholesterol groups (p = 0.839 and p = 0.641, respectively). The other variables associated with prolonged PFS at the univariate analyses were: ECOG PS = 0, absence of hypertriglyceridemia in the medical history, no antibiotic nor steroid therapy within 30 days before the starting of immunotherapy, absence of liver, bone or brain metastatic lesions, complete/partial response or stable disease to the previous line of therapy, HDL cholesterol > 50 mg/dl and absence of pleural effusion and/or ascites. No statistically significant difference in PFS was found for patients with BMI > 25 compared to those with BMI ≤ 25.

The multivariate analysis confirmed the positive prognostic role of ECOG PS = 0, no steroid nor antibiotic therapy within 30 days before the first cycle of ICIs, absence of bone lesions and of

pleural and/or ascites. High baseline cholesterol was not confirmed as prognostic factor for PFS at the multivariate analysis. All the details of univariate and multivariate analysis are summarized in Table 4 and 5.

Discussion

In the present study, we reported for the first time in the literature, to the best of our knowledge, that patients with advanced cancer and high cholesterol levels before ICI administration have prolonged OS and PFS to immunotherapy compared to those of patients with low cholesterol. Multivariate analyses confirmed the prognostic role of hypercholesterolemia in terms of OS but not of PFS; even landmark analyses at 6 and 12-months for PFS did not show differences between high and low cholesterol level groups. Probably PFS is not a good surrogate for efficacy in the case of ICI treatment [39-40]. Intriguingly, the positive prognostic value of baseline hypercholesterolemia on OS seems to be independent from statin use, antibiotic therapies, primary tumor and line of therapy.

Despite the established association between diabetes mellitus and dyslipidemia [41], patients with high cholesterol in our study population did not have hyperglycemia or hypertriglyceridemia. This result is unexpected and difficult to explain.

Our data are consistent with the preliminary results (abstract e20691) presented during the 2019 ASCO annual meeting by Galli and colleagues: they conducted a retrospective study in 55 patients with metastatic NSCLC treated with ICI immunotherapy, reporting a positive correlation between plasmatic cholesterol levels and clinical outcomes [42]. The study population was limited and selected, on the contrary in our study, we provided a wider sample size and a more heterogeneous population.

The relationship between metabolic disorders and immune system has been previously explored [28,43]. It is known that the metabolic syndrome, that includes hypercholesterolemia, is characterized

by a continuous efflux of inflammatory cytokines and chemokines [44]. Hypercholesterolemia, as prolonged chronic inflammation status, stimulates the proliferation of hematopoietic precursor cells in bone marrow and gives rise to myeloid-derived suppressor cells (MDSCs) through a mechanism known as "emergency granulo-monocytopoiesis" [44-46]. MDSCs include two subsets: monocytic MDCSs (M-MDSCs) and granulocytic MDSCs (PMN-MDSCs). M-MDSCs and PMN-MDSCs are immature myeloid cells that have acquired immunosuppressive activities, including the overexpression of PD-L1 [46,47]. Moreover, during emergency granulo-monocytopoiesis, terminal differentiation and M2 polarization of tumor-associated macrophages (TAMs) occurs [44,48]. MDSCs and TAMs enrich the tumor micro-environment. The tumor itself releases cytokines that increase MDSCs and TAMs mobilization and infiltration within the tumor mass [44].

We could hypothesize that hypercholesterolemia, as low-grade inflammatory condition, may facilitate the proliferation and the migration of TAMs and MDSCs to the tumor microenvironment. Although TAMs and MDSCs have immunosuppressive activities, we may only speculate that the overexpression of PD-L1 from MDSCs could render ICIs more effective. Indeed, MDSCs and TAMs have been associated with poor outcome with ICIs therapy [49], because they release many suppressive factors that likely overcome other immune favorable factors. Therefore, no conclusive considerations about the role of TAMs and MDSCs in hypercholesterolemia status can be drawn.

As known, cholesterol is able to induce a conformational change of the transmembrane domain of MHC II, confirming its immunomodulation role [50].

Apolipoprotein E (ApoE), a fat binding protein transporting lipids, fat-soluble vitamins and cholesterol, is involved in the processing of lipid antigens by antigen presenting cells (APC) for recognition by natural killer T cells, which secrete cytokines and start the immune response [51]. *ApoE* gene and several lipid transporters genes have been included in serum protein signatures to identify patient responders to immunotherapy [52]. Similarly, baseline cholesterol levels could be included, together with other cited biomarkers, as a component of an inflammatory index.

Our results do not allow to understand if hypercholesterolemia is directly able to improve the outcome in patients treated with ICI or if it simply reflects the inflammatory status of patients, reflecting tumors more likely to respond to immunotherapy.

As expected, the absence of pleural effusion and/or ascites was associated with prolonged OS and PFS both at univariate and multivariate analysis, since these conditions represent particularly aggressive cancers that are known to be associated with disease complications and poor outcome irrespective of the type of treatment received. Perhaps, these data may also be explained as "third space" effect, leading to the sequestration and to the lower bioavailability of the drugs. Consistently with the literature, in our study population no antibiotic therapy within 30 days before ICI and ECOG PS = 0 were associated with good oncological outcomes [53-54].

Regarding the statin use, we have observed that patients treated with statins had higher OS and PFS compared to patients did not treat with statins, although the difference was not statistically significant for PFS. This result is in agreement with a recent observational study conducted on 67 patients affected by NSCLC and treated with Nivolumab by Omori and colleagues. Patients who were administered statins showed better response rate compared to patients who were not administered the same drugs. A major limitation of the above study is that the cholesterol levels were unknown [55].

Obesity is another disorder included in the metabolic syndrome. Recent studies have demonstrated that overweight cancer patients treated with ICIs had prolonged OS and PFS compared to those of non-overweight patients, probably because of the capacity of white adipose tissue to modulate the immune response [26]. Consistently to these data, a concordance between higher BMI and good clinical outcomes was found in our study, but the difference was not statically significant, probably due to the limited sample size. Moreover, diabetes seemed to have a positive impact, confirming a close correlation between metabolic syndrome and response to immunotherapy [56].

Our study has several limitations, including the retrospective design, the small sample size, the selection bias due to the availability of a cholesterol test for inclusion, the heterogeneity of the population in terms of primary tumors and immunotherapy treatment line (although we have included these variables in the multivariate analyses in order to mitigate the bias) and the lack of a control group of patients not receiving ICIs. On the other hand, we investigated the prognostic role of cholesterol in a "real life" population.

Further prospective studies should be carried out in order to confirm the usefulness of plasmatic cholesterol levels assessed immediately before ICIs to possibly identify patients more likely to respond to immunotherapy.

Figure Legends

Supplementary Figure 1. Overall survival in overall population

Figure 1. Overall survival according to baseline cholesterol levels

Supplementary Figure 2. Progression free survival in overall population

Figure 2. Progression free survival according to baseline cholesterol levels

Table Legends

Table 1. Baseline patients characteristcs

Table 2. Univariate analysis for overall survival

Table 3. Multivariate analysis for overall survival

Table 4. Univariate analysis for progression free survival

Table 5. Multivariate analysis for progression free survival

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