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MDPI

Personalized dietary intervention based on Mediterranean diet as a complementary strategy to modify gut microbiome, quality of life and outcomes in patients with metastatic melanoma treated with immunotherapy: a study protocol.

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Abstract: Not all cancer patients respond to immunotherapy, and the variation in response may be attributed to the individual's microbiome, which is profoundly influenced by dietary habits. Understanding and manipulating the microbiome through dietary interventions offers a potential avenue for enhancing immunotherapy outcomes in cancer patients and consequently may serve as a complementary therapeutic strategy. Bearing in mind the latter as well as our previous research on the importance of gut microbiome as a co-denominator for immunotherapy response, we aimed towards constructing this study protocol on personalized dietary intervention based on Mediterranean diet as a complementary strategy to modify gut microbiome, quality of life and outcomes in patients with metastatic melanoma treated with immunotherapy. The present protocol hypothesis is that remote intervention with MD will be achievable, and would positively affect all the aforementioned parameters. The potential gains of this study protocol and upcoming research extend to enhancing quality of life outcomes and the survival rates of patients with metastatic melanoma, since it could also result in reinforcement of the recommendations of nutritional intervention as a crucial component of cancer treatment.

Keywords: dietary intervention; immunotherapy; Mediterranean diet; microbiome; short-chain fatty acids; study protocol

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1. Background

Metastatic melanoma is a malignant tumor of melanocyte origin that has spread to other organs. The basis of treatment is systemic therapy, most commonly anti-programmed death-1 (PD-1) and anti- cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) immunotherapy, although for some patients, thyrosine kinase inhibition is also a treatment option [1]. Survival of metastatic melanoma patients has been significantly extended over the last decade, and the use of immunotherapy has led to a median overall survival

of 72 months and a response rate of up to 60% [2]. However, not all cancer patients respond equally to immunotherapy, and the variation in response may be attributed to the individual's microbiome, which is heavily influenced by dietary habits [3]. Over 2/3 of patients will progress during the 6.5 years of follow-up and currently there is a limited number prognostic and predictive parameters to assess the response to immunotherapy [2]. However, understanding and manipulating the microbiome through dietary interventions offers a potential avenue for enhancing immunotherapy outcomes in cancer patients and consequently may serve as a complementary therapeutic strategy.

Due to previous data, as well as our own publication on the importance of gut microbiome as a co-denominator for immunotherapy response [4], and aiming towards constructing a protocol on dietary intervention for enhancing immunotherapy response in metastatic melanoma patients, we performed a systematic review according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. We identified a total of 2130 citations through searching PubMed/Medline using the following search strategy: ((food) OR (diet*) OR (nutri*)) AND (immunother*) AND ((butyrate) OR (SCFA) OR (microbio*)) AND (cancer). Animal studies, studies with pariticipants aged <18 yr., review articles, case reports, book chapters and publications before 2015 yr. were not within our scope. Since we did not identify any relevant investigational studies we proceeded with exploring diet-microbiome-immunotherapy axis through hand-searching and analysing the secondary/indirect evidence.

Different dietary habits can influence the abundance and diversity of microorganisms within the gut. A diet with moderately elevated sodium use (2.3-4 g daily) [5], diet rich in fiber (20-25 g daily) [6], fruits and vegetables (≥5 servings daily) [7], vitamin D [8], omega-3 fatty acids [9] and whole grains (≥3 servings daily) [10] has been associated with a more diverse and beneficial microbiome, which in turn promotes the production of short-chain fatty acids (SCFA).

All the listed foods belong to the Mediterranean diet (MD), which is based on fresh fruits and vegetables, legumes, olive oil, and unrefined fiber. MD also includes a lower intake of meat, eggs, processed foods, sugars, and saturated fatty acids, which may all lead to a less diverse and potentially less favorable microbiome and health outcomes. Various clinical studies already demonstrated the beneficial effect of MD in non-oncology patients [11] As for oncology patients, the benefit of the MD in reducing the incidence of cancer has been known for many years [12], especially for breast cancer patients [13]. Furthermore, a published cohort study with 52 patients receiving immune checkpoint blockade (ICB) treatment for various solid tumors revealed that higher fecal SCFA concentrations were associated with longer progression-free survival [14]. Another cohort study comprising 91 patients with advanced melanoma in the UK and the Netherlands, demonstrated that a stronger adherence to the MD principles was linked to a higher likelihood of responding positively to ICB treatment [15]. However, there is a scarcity of randomized trials evaluating the effect of the nutritional intervention based on the MD in cancer patients undergoing treatment. As far as we know, there are no current clinical trials applying a nutritional intervention based on the MD in patients with metastatic melanoma; however, there is an ongoing randomized DIET study - NCT04645680 (with expected ending in 2024), aiming to evaluate effectiveness of fiber-enriched diet within the melanoma setting [16].

The potential effect of the MD based nutritional intervention could result in a greater benefit compared to trials focusing only on one nutrient. Considering the issues learned from COVID-19 pandemic [17], the main goal of our trial is to determine the effectiveness and applicability of a remote personalized nutritional intervention based on the MD to increase the intake of micronutrients (flavones, anthocyanins, omega-3 fatty acids, vitamin D and fiber) previously associated with a positive response to immunotherapy. Additionally, there is a scarce body of literature discussing the intricate interplay between the microbiome and immune system, suggesting that specific microbiome signatures pro-

ducing essential metabolites such as SCFAs may enhance the effectiveness of immunotherapy and regulate the activity of immune cells not only by triggering metabolic and epigenetic reprogramming but also by binding to cognate receptors on the surface of cells. Hence, an evaluation of the changes in gut microbiome following a MD based remote intervention, particularly of SCFA producing bacteria is also one of the goals of this research.

2. Methods

We designed a protocol for a 12-week, 2-arm, parallel group, randomized pilot trial to determine the effectiveness of remotely-delivered personalized nutritional intervention. The study would also be single-blinded as the researchers, except the nutritionists, will not know whether the subjects are in the intervention or control group. The research will be conducted in accordance with the Declaration of Helsinki and the Principles of Good clinical practice (GCP).

We would apply the following inclusion criteria: i) age ≥18 years, ii) patohistologically confirmed melanoma stage IV or inoperable stage IIIC, with radiological measurable disease on computerized tomography (CT) or positron emission tomography (PET)/CT, for which the multidisciplinary team recommended initiation of treatment with mono or dual immunotherapy with anti-PD-1 and/or combination antiPD-1 + anti-CTLA4 immunotherapy, iii) written informed consent prior to participation, willingness for monitoring and adjustment of the dietary regimen if necessary, and iv) Eastern Cooperative Oncology Group (ECOG) status 0-1.

On the other hand, lifetime history of psychiatric disorders, active brain metastases, active autoimmune disease, systemic use of equal or more than 10 mg of prednisone or an appropriate corticosteroid equivalent during screening, exposure to antibiotics and probiotics or other supplements that can affect the study outcome during screening within the last 3 weeks, uncontrolled diabetes, history of clinically significant drug or alcohol abuse within the last 6 months, specific dietary habits that are not inclined or able to change or the existence of food allergy or intolerance to certain food or inability or refusal to participate in all research procedures, would all be exclusion criteria.

Patients will then be randomized (web-based randomization service) to the control and intervention groups. The control group will continue with their usual/current diet, with the exception of supplementation of those in whom low serum vitamin D level (in accordance with current medical recommendations)

The intervention study will involve scheduled communications (via phone, video call, and/or email) with a trained nutritionist based on protocol-determined parameters and recommendations, organized weekly in the first month, every other week in the second month, and once a month in the third month. Each patient will receive general guidance and information about the MD. Additionally, a personalized nutritional plan based on the MD will be prepared for each patient, considering their initial dietary habits, preferences, food accessibility, and financial constraints. Throughout the 12-week period, patients will be motivated to adhere to the prescribed dietary regimen. The values of specific dietary parameters aimed to be achieved with the MD intervention is given in Table 1.

Table 1. Values of specific dietary parameters aimed to be achieved with implementing the personalized dietary intervention based on Mediterranean diet.

	Dietary parameters	***References***
Flavonoides	> 9 mg /day	[18,19]
Anthocyanins	> 260 mg /day	[20]

Proteins %	> 100 % < 150 % recommended daily intake g/kg BM *above 1 g/kg/day and, if possible up to 1.5 g/kg/day*	[21]
Omega 3	>250 mg /day	[22]
SFAs	as low as possible *(e.g. < 12% of EI (energy intake))*	[21,23]
Fruits and Vegetables	at least 5 servings/day	[21,24]
Foods with added sugar	< 20g daily or as low as possible	[25]
Fibers	> 20 g daily	[6]
Salt (Sodium)	No restrictions*	[5,26]

saturated fatty acids – SFAs . *in absence of high cardiovascular risk.

Besides having tele-consultation with the nutritionist, there will be no other interventions in any group; what is more, participation in the study will not influence the selection of treatment modalities. Treatment selection will be exclusively based on the recommendations by the multidisciplinary tumor board. Given that this is a pilot study, and we do not have an estimate of the required sample size, 15 patients per group will be selected, which represents the previously analyzed number of patients where a difference in microbiome and diet was found [4].

All the patients will be evaluated on the baseline with PET/ or CT, biomarkers of melanoma (S100, lactate dehydrogenase), Croatian version of European Organization for Research and Treatment of Cancer Quality of life questionnaire (EORTC QLQ-C30 [27]), food-frequency questionnaire (FFQ), 3x 24-hour dietary recall, and the analysis of faecal microbiome. The same parameters will be evaluated 3 months later, after completion of initial immunotherapy, as presented in Table 2.

Table 2. Study schematic on the intervention and follow-up strategies.

	screen/ baseline	**week 1**	**week 2**	**week 3**	**week 4**	**week 8**	**week 12**	**follow up (12 months)**
PET/CT or CT	x						x	x
laboratory testing	x						x	x
3x24h recall	x				x	x	x	
FFQ	x						x	
anthropometrics	x						x	
stool sample	x						x	
consultation with nutritionist	x	x	x	x	x	x	x	

computerized tomograpy – CT ; food frequency questionnaire – FFQ ; positron emission tomography – PET.

Laboratory testing will involve blood samples and determine complete blood count with LDH, S100, CRP, vitamin D, and albumin.

The fecal analysis will be conducted using OMNIgene OM200 containers, and microbial DNA will be subjected to metagenomic analysis through the Illumina NextSeq 2000 platform (2 x 150 kb). Microbiome analysis will be performed on Illumina NextGen devices following prior preparation. Alpha-diversity (Shannon) and beta-diversity (CHAO1) analyses will be conducted, along with LEfSE analysis to identify bacterial differences among groups. Pearson and Spearman correlations will be employed to correlate parameters at the beginning and end of the study.

The assessment of radiological response will be obtained using the iRECIST criteria [28], with the analysis of differences using the chi-square or Fisher's exact test. During further follow-up, time to progression-free survival (PFS) and overall survival (OS) will also be analyzed using the Kaplan-Meier method and compared between groups using the log-rank test. The questionnaire EORTC QLQ-C30, consisting of 30 questions assessed using a Likert scale, will be analyzed according to the EORTC guidelines. The incidence of adverse events will be evaluated according to the CTCAE classification [29] and calculated using percentages and frequency analysis.

ClinicalTrials.gov trial registration will be conducted upon receiving the confirmation from the Ethical Committee.

3. Brief discussion

This study protocol and the following trial is important as it will provide data on understanding and manipulating the gut microbiome through dietary intervention (MD) as a complementary therapeutic strategies, offering a potential avenue for enhancing immunotherapy and quality of life outcomes in cancer patients.

This study will not be without limitations, and obtained results will need to be interpreted accordingly (e.g. single-blinded, single-centre, recall-bias, external validity). To the best of our knowledge, this is going to be the pioneer study evaluating the personalized dietary intervention based on MD as a complementary strategy to modify gut microbiome, quality of life and outcomes in patients with metastatic melanoma treated with immunotherapy, which we see as a strength. However, the latter also goes alongside limitation since power-analysis and study sample size calculation, in absence of body of evidence, could not be performed / not applicable. It's important to note that the quality of a pilot trial can be substantial, even with limitations such as a small sample size. Despite this, the insights gained from this pilot trial protocol and upcoming research will pave the way for the design of a study with a larger number of participants.

4. Conclusion

We hypothesize that remote intervention with MD will be achievable, and would positively affect all the aforementioned parameters, based on previous research. The profound understanding of the complex relationship between diet, SCFAs, and immunotherapy response holds great promise for developing personalized dietary approaches to cancer immunotherapy-containing treatment regimens. To deduce, by elucidating the mechanisms involved and identifying concrete personalized dietary strategies that optimize gut microbiome, it may be possible to further enhance the effectiveness of immunotherapy, offer novel therapeutic approaches for cancer patients, and improve their quality of life. Last but not least, the potential gains from this research extend to enhancing quality of life outcomes and the survival rates of patients with metastatic melanoma. This could also reinforce the recommendation of nutritional intervention as a crucial component of treatment.

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