PROJECT 1

DoS: Prof. Lorenzo DAGNA

Title: Evaluation of prognostic factors associated with the occurrence of immune-related adverse events in oncologic patients treated with immune-checkpoint inhibitors

Curriculum: Experimental and Clinical Medicine

Residency Program: Allergy & Clinical Immunology

Link to OSR/UniSR personal page:
https://www.hsr.it/clinica/specialita-cliniche/immunologia-reumatologia-allergologia-e-malattie-rare/lorenzo-dagna/
http://www.unisr.it/k-teacher/dagna-lorenzo/

Project description (*Number of characters*, *including spaces*: 2.000 - 3.000)

Immune-checkpoint inhibitors (ICIs) enhance anti-tumor immune responses by breaking immune tolerance. The advent of these drugs has once again re-exposed the association between cancer and autoimmunity, which has long fascinated scientists [1]. Specifically, individual predisposition to autoimmunity is often revealed when ICIs unleash antitumor immune responses, thus inducing in predisposed patients a broad variety of inflammatory and autoimmune side effects (immune-related adverse events, IRAEs). Common IRAEs include skin manifestations, endocrine disorders, and inflammatory bowel diseases. In some cases, IRAEs can occur in the form of systemic autoimmune diseases (e.g., inflammatory arthritis, myositis, systemic vasculitis) [2,3]. Critical unanswered questions and related unmet needs include: I) the identification of patients who are more likely to respond to treatment with ICIs; II) the identification of biomarkers to predict or reveal clinically meaningful antitumor immune responses; III) the identification of patients who are at higher risk of developing IRAEs; IV) the relationship between the development of IRAEs and of clinically meaningful responses to treatment with ICIs; V) the feasibility of treatment in patients with a history of autoimmunity; VI) the optimal clinical management of patients with IRAEs [1].

Recently, the presence of some preexisting antibodies has been associated with both clinical benefit and the development of irAEs. In order to further confirm this hypothesis, we aim to identify biomarkers of latent autoimmune activation, which can suitably be used to predict development of IRAEs. To do so, the following parameters will be prospectively evaluated in patients undergoing treatment with ICIs: I) full clinical and family history (i.e., family history or past personal history of systemic autoimmune diseases); II) full immune-rheumatologic examination; III) extensive immune profiling; IV) immunophenotyping of circulating T lymphocytes; IV) HLA genotyping and determination of haplotypes associated with risk of developing autoimmune diseases. Patients will be prospectively evaluated, stringently followed-up, and monitored for the development of changes in the aforementioned parameters or the development of IRAEs. Response to different available therapeutic options will also be explored.

Investigations aimed at determining the individual immune response to cancer hold clear translational relevance. For example, patient HLA and serum autoantibody profiling may predict the predisposition to develop either effective antitumor immune response or severe IRAEs, thus setting the basis for individualized

approaches to cancer immunotherapy with ICIs. However, theoretical implications of this study reach beyond clinical management, and might embrace the understanding of individual immunological differences in the development of cancer and in the response to cancer therapies, particularly treatment with ICIs.

Skills to be acquired by the student: Perform independent literature search, study planning, pose a research question/problem, examine the range of available modes of inquiry, identify the appropriate research mode and procedure, identify a data collection strategy. Acquire advanced knowledge of clinical immunotyping, its analysis and clinical/research relevance. Develop independent ability to analyze, interpret data, and draw conclusion from data, and to write a research paper.

References (max. 3)

[1] Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade, N Engl J Med (2018)

[2] Calabrese LH, Calabrese C, Cappelli LC. Rheumatic immune-related adverse events from cancer immunotherapy, Nat Rev Rheumatol (2018)

[3] Tomelleri A, Campochiaro C, De Luca G, Cavalli G, Dagna L. Anti-PD1 therapy-associated cutaneous leucocytoclastic vasculitis: A case series. Eur J Intern Med (2018)