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TOXICITIES OF SINGLE AGENT AND COMBINATION IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WITH PRE-EXISTING AUTOIMMUNE DISEASES

¹Sabina Sandigursky, ²Safa Houssein, ³Xerxes Pundole, ⁴Elizaveta Efuni, ⁴Samuel Cytryn, ⁵Maryam Buni, ⁵Anna Pavlick, ⁴Michelle Krogsgaard, ³Chantal Saberian, ³Mehmet Altan, ³Maria Suarez-Almazor, ⁴Jeffrey Weber, ³Adi Diab, ³Noha Abdel-Wahab*. ¹NYU Langone Health; ²Montefiore Medical Center, Bronx, NY, USA; ³MD Anderson, Houston, TX, USA; ⁴NYU Langone, New York, NY, USA; ⁵Cornell Medical Center, New York, NY, USA

Background Autoimmunity is associated with increased risk of malignancy. However, patients with pre-existing autoimmune diseases (AIDs) were excluded from immune checkpoint inhibitor (ICI) trials as these agents can cause immune-related adverse events (irAEs). Data are limited on the safety and efficacy of combination immunotherapy in this at-risk population.

Methods We conducted a multi-center retrospective study to evaluate the safety and efficacy of ICI therapy in patients with pre-existing AID treated at NYU and at MD Anderson Cancer Center. Primary endpoints were occurrence of irAEs and AID flares. Secondary endpoints were time to treatment failure (TTF) and overall survival (OS).

Results Of 121 patients identified from our institutional databases, 53% received single-agent anti-PD-1 therapy, and 47% received ICI combination. Over half of malignancies were lung cancer (34%) and melanoma (20%). Preexisting AIDs included: rheumatologic (58%), gastrointestinal (12%), endocrine (16%) and neurologic (4%). Overall, 94% had asymptomatic AID, and 21% were receiving systemic immunomodulatory drugs at ICI initiation. Median duration of follow up after ICI initiation was 9 (0.4–41.9) months in patients receiving ICI combination and 8 (0.2–47.3) months in patients receiving anti-PD-1 monotherapy. Combination therapy was associated with higher rates of irAEs compared with anti-PD-1 monotherapy (56% versus 28%). Grade 3/4 irAEs were equivalent in both groups: combination (38%) and anti-PD-1 group (39%). Treatment related deaths were not observed in any group. AID flares occurred in 36% of the anti-PD-1 group versus 29% of combination group. Adverse events (irAEs and/or flares) required systemic immunomodulatory therapies more frequently in the combination group (84%) versus the anti-PD-1 group (59%), and permanent ICI discontinuation was reported in 19% of patients in the combination group versus 11% in the anti-PD-1 group. Tumor progression was observed in 49% of patients on combination ICI and TTF was 14.5 months (95% CI 0.000–31.5), while progression was observed in 64% of patients on anti-PD-1 monotherapy and TTF was 6.4 months (95% CI 4.01–8.9) ($p=0.019$). Median OS in the combination therapy group was not reached whereas it was 27.3 months in the anti-PD-1 monotherapy group.

Conclusions Our novel findings suggest that high rates of adverse events were observed in patients with pre-existing AIDs treated with ICI combination therapy. However, they were manageable and rarely required permanent ICI discontinuation. Taken together, these data show that ICIs should be offered, albeit with caution in patients with AIDs, to achieve durable cancer remission. Prospective clinical data are needed to guide these complex decisions.

Ethics Approval The study was approved by NYU Langone's Ethics Board, approval number i18-01657 and MD Anderson's Ethics Board, approval number PA19-0089

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BLOCKING CYTOKINE IL-1 WITH ANAKINRA FOR THE PREVENTION OF CYTOKINE RELEASE SYNDROME IN COVID-19

¹Erik Soule, ²Jason Williams*, ³Matthias Piesche. ¹University of Florida College of Medicine; ²Williams Cancer Institute, Atlanta, Georgia, USA; ³Catholic University of Maule, Talca, Chile

Background The novel coronavirus, known as SARS-CoV-2, or COVID-19 became a pandemic in early 2020, causing significant human suffering and economic woes globally. The pathophysiology of acute respiratory failure may be related to a robust immune reaction against the virally infected cells (figure 1). This mechanism is molecularly similar to that of cytokine release syndrome, which is mediated by cytokine IL-1 and can be seen as a complication of immunotherapy.

Methods Clinical data from cancer patients treated for cytokine release syndrome were collected from an interventional oncology practice and retrospective analysis was performed.

Results Five patients were treated for cytokine release syndrome related to administration of immunotherapy agents. Symptoms included hypotension, loss of consciousness, fever, headache, and respiratory failure. Three of these patients were treated with anakinra, with abrogation of symptoms of cytokine release syndrome (table 1). The remaining two patients

Abstract 659 Figure 1 Imaging findings of COVID-19 viral pneumonia

Axial, and coronal computed tomography images in a patient with laboratory proven COVID-19 infection demonstrating diffuse ground glass opacities in a peripheral and peribronchovascular distribution interspersed with areas of frank consolidation.

Abstract 659 Table 1 Anakinra cohort

Three patients who experienced clinical signs and symptoms of cytokine release syndrome after administration of immunotherapy. These patients were treated with anakinra, and survived.

Table 1. Clinical characteristics of patients treated with anakinra to inhibit CRS.

Characteristics	Patient 1	Patient 2	Patient 3
Age	67	69	73
Sex	Male	Female	Male
Underlying malignancy	Stage 4 renal cell carcinoma	Stage 4 ovarian cancer	Stage 4 prostate cancer
Treatment administered	Intratumoral OX40, CpG, ipilimumab	Intratumoral ipilimumab, nivolumab, IL-2	Intratumoral OX40, CpG, ipilimumab
Symptoms of cytokine release syndrome	Hypotension (60/20), fever, dyspnea, headache	Hypotension, headache, loss of consciousness, bilateral temporo-parietal regional hypodensities on head CT	Hypotension (70/40), fever, loss of consciousness
Treatment for cytokine release syndrome	Anakinra 100 mg subcutaneous injection, single dose	Anakinra 100 mg subcutaneous injection, daily for 5 days	Anakinra 100 mg subcutaneous injection, daily for 2 days
Clinical course	Complete resolution in 12 hours	Patient became cognitively intact with residual right upper and lower extremity paralysis	Complete resolution in 72 hours
Outcome	Survived without sequelae	Discharged to hospice with residual paraplegia	Survived without sequelae

Abstract 659 Table 2 Glucocorticoids cohort

Two patients who experienced clinical signs and symptoms of cytokine release syndrome after administration of immunotherapy. These patients were treated with glucocorticoids, tacrolimus, and supportive measures, and subsequently died.

Table 2. Clinical characteristics of patients treated with glucocorticoids to inhibit CRS.		
Characteristics	Patient 1	Patient 2
Age	68	59
Sex	Male	Male
Underlying malignancy	Stage 4 GIST*	Stage 4 colorectal cancer
Treatment administered	Ipilimumab, nivolumab, cryoablation	Intratumoral ipilimumab, nivolumab, CpG
Symptoms of cytokine release syndrome	Hypotension, loss of consciousness, renal failure, respiratory failure	Hypotension, loss of consciousness, respiratory failure, myocarditis
Treatment for cytokine release syndrome	Prednisone 1000 mg daily, tacrolimus, vasopressors, dialysis, intubation and mechanical ventilation	Prednisone 1000 mg daily, tacrolimus, vasopressors, intubation and mechanical ventilation
Clinical course	Non responsive to treatment	Progressive symptoms of CRS
Outcome	Death	Death

received glucocorticoids, vasopressors, and respiratory support, suffering progressive symptoms of cytokine release syndrome, and death (table 2).

Conclusions The IL-1 inhibitor, anakinra, has shown efficacy in ameliorating signs and symptoms of cytokine release syndrome caused by immunotherapy administration. Mechanistic similarities between cytokine release syndrome and COVID-19 related pulmonary damage suggest that this pharmacotherapeutic intervention could decrease mortality and need for mechanical ventilation in patients infected with COVID-19.

Consent Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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Machine learning, artificial intelligence, and computational modeling

660 DEVELOPING GENERALIZABLE DEEP LEARNING MODELS FOR TUMOR SEGMENTATION IN PATHOLOGY IMAGES TO ENABLE THE IDENTIFICATION OF PREDICTIVE BIOMARKERS FOR IMMUNOTHERAPIES

Qinle Ba*, Peng Yang, Jennifer Yearley. Merck, Kenilworth, CA, USA

Background Despite recent advances in cancer immunotherapies, their efficacies vary significantly among patients. To better understand the mechanisms of drug resistance, it is essential to characterize immune responses to immunotherapies in the tumor immune microenvironment (TME) from intact patient tissues. To this end, quantitative spatial immune profiling of pathology images has been the focus for many recent studies. Such analysis often depends critically on the automated image segmentation of tumor and stromal compartments. However, current segmentation approaches, even these based on deep learning, often fail to perform well when given datasets to segment, which differ from the data on which they were trained. Specifically, tissue segmentation models trained for one type of organ (source) face challenges in performance when applied directly to images of another organ type (target), even when the targeted regions to segment are highly similar in morphology between the source and target.

Here, we present a segmentation approach to adapt knowledge learned from source data of one cancer type to unlabeled target data of another organ cancer type via unsupervised domain adaptation (UDA) frameworks. This research will help build deep learning models that significantly reduce the need for expert manual annotations.

Methods Annotated colorectal cancer (CRC)¹ (target domain) and prostate cancer (source domain)² were used for tumor tissue segmentation model development, containing image tiles from 38 and 20 whole slide images, respectively. We compared the performance and robustness of four approaches. First, we implemented two output-space domain-adversarial based UDA's. We then implemented a self-training-based approach. Additionally, we designed a two-stage UDA approach by first conducting self-training and then further aligning target domain features with category-anchors generated from source data after a first stage of self-training.

Results Directly applying a tumor tissue segmentation model trained on prostate cancer images (source) to CRC images (target) resulted in an intersection-over-union (IOU) score of 62.5%, which was 19% IOU lower (domain gap) than using a model trained on target data. Methods based on output-space domain adversarial training reduced the domain gap by up to 8% IOU, a performance result which was better than with self-training-based methods, which only reduced the domain gap by 4%. Both sets of approaches improved precision by 10%.

Conclusions We demonstrate the feasibility of designing tumor segmentation models that are robust and generalizable to multiple indications. The UDA approaches have the potential to speed our understanding of factors influencing immunotherapy efficacy through automated annotation of tissue regions required.

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661 FIVE IMMUNOTYPIC SIGNATURES IDENTIFIED IN HUMAN GLIOBLASTOMA CORRELATE WITH TUMOR CONTACT WITH THE LATERAL VENTRICLE, IMMUNE SUPPRESSION, AND PATIENT OUTCOME

Todd Bartkowiak*, Sierra Barone, Madeline Hayes, Allison Greenplate, Justine Sinnaeve, Nalin Leelatian, Akshikumar Mistry, Caroline Roe, Bret Mobley, Lola Chambliss, Reid Thompson, Kyle Weaver, Rebecca Ihrie, Jonathan Irish. Vanderbilt University Medical Center, Nashville, TN, USA

Background Glioblastomas make up more than 60% of adult primary brain tumors and carry a median survival of less than 15 months despite aggressive therapy. Immunotherapy, now standard of care for many peripheral solid tumors, offers an appealing alternative platform that may improve survival outcomes for patients with glioblastoma; however, predictive features that could inform responsiveness to different immunotherapeutic modalities remains to be elucidated. Recent studies have demonstrated that patients whose tumors show radiographic contact with the lateral ventricle have diminished