Conclusions ICI is associated with a high incidence of TE in patients with melanoma; TE is associated with substantial worsening of survival.

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651 NEUROLOGICAL ADVERSE EVENTS ASSOCIATED WITH IMMUNE CHECKPOINT INHIBITORS: OUR EXPERIENCE IN A TERTIARY CARE CENTER

Pablo Alvarez-Ballesteros*, Javier Buisan-Catevilla, Alvaro Beltrán-Corbellini, Iligio Corral-Corral, Javier Pozas-Perez, Victor Albanan-Fernandez, Lucia Sanz-Gomez, Jorge Esteban-Villarrubia, Javier Torres-Jimenez, Jesús Chamorro-Perez, Diana Rosero-Rodriguez, Maria San Román-Gil, Aihara Sonia-Rivas. Ramon y Cajal University Hospital, Madrid, Spain

Background Immune checkpoint inhibitors (ICIs) have become a revolution in the treatment of many tumoral diseases, resulting in a significant increase in terms of life expectancy and quality of life. Despite these outstanding advances in long-life survival, a new spectrum of adverse events has been developed and is known to be one of the biggest challenges in clinical practice nowadays. Immune-mediated neurotoxicity stands out as a rather unusual complication, but its potentially lethal consequences make the characterization and right management of this adverse event a crucial issue in this field.

Methods This is a retrospective study including all the cancer patients that have developed any neurological adverse event related to ICIs treatment, in a period of 4 years (from 2017 to 2020).

Results 13 patients were included in the study (8 were treated with antiPD-1/PD-L1 immunotherapy, 1 with antiCTLA-4 and 4 with the combination of both strategies). 4 patients developed generalized myasthenia gravis (GMG), 4 immune-mediated encephalitis (IME), 3 immune-related encephalopathy without radiological/analytical evidence of encephalitis, 1 mixed-polyneuropathy, and 1 polymyositis. 3 patients with GMG were referred to other specialties. Twelve patients (40%) presented a favourable clinical outcome. In severe cases, an improvement of steroids for their irAE, however only a small majority of patients required higher level care (i.e ED or admission) than was able to be provided in the clinic. Twenty-two patients (73%) required steroids as their irAE management of this adverse event a crucial issue in this field.

Conclusions Herein we present early data from an acute care APP led CPI outpatient clinic. Most patients required initiation of steroids for their irAE, however only a small majority required higher level of care and were able to be managed as an outpatient. We acknowledge that while our cohort of patients is small, it does provide early evidence of the utility of a CPI acute care clinic and additional hypothesis generating clinical questions.

Ethics Approval This study was approved by the institutional review board at Mayo Clinic.

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652 EARLY OUTCOMES OF AN APP ACUTE CHECKPOINT INHIBITOR (CPI) CARE CLINIC

Lisa Kottschade*, Casey Fazer, Anna Schwecke. Mayo Clinic, Rochester, MN, USA

Background Checkpoint inhibitors continue to be used for a wide variety of oncologic and hematologic indications. Early recognition and intervention is crucial to prevent significant morbidity and/or mortality from immune related adverse events (irAE’s). Physicians and APPs outside of hematology/oncology practices are generally not familiar with these types of side effects which may lead to treatment delays, and inappropriate management. We recently identified this as a gap in continuity of care amongst patients undergoing CPI therapy for their malignancy, and therefore developed a CPI acute care outpatient clinic, designed to meet this need.

Methods Starting April 2020, we developed an CPI focused management clinic led by 3 APPs to provide outpatient irAE management 5 days a week. Three types of needs were identified: acute (within 24 hours), post hospitalization (within 48 hours of discharge), and long term follow-up (high grade irAE).

Results From April 24–August 24, 2020 our CPI clinic had a total of 50 visits (30 unique patients). Given that many patients to our practice are from > 2 hours away, as well as the constraints of the current pandemic, visits were conducted as in person, video consult (telemedicine), or phone. The most common regimens for patients were PD-1 alone (10), PD-1 + targeted (7), dual CPI (6), PD-1 + chemotherapy, and clinical trial, PD-L1 alone, PD-L1 + chemotherapy (1 each). The top three types of malignancies seen were melanoma (7), lung (6) and gynecological (4). The most common irAE referral reason was hepatitis (8), diarrhea/colicitis (6) and thyroiditis (4). Only three patients (10%) required higher level care (i.e ED or admission) than was able to be provided in the clinic. Twenty-two patients (73%) required steroids as their initial treatment for irAE, with 4 patients (13%) requiring referral to other specialties. Twelve patients (40%) presented with ≥2 irAE’s at the time of being seen in clinic.

Conclusions Herein we present early data from an acute care APP led CPI outpatient clinic. Most patients required initiation of steroids for their irAE, however only a small majority required higher level of care and were able to be managed as an outpatient. We acknowledge that while our cohort of patients is small, it does provide early evidence of the utility of a CPI acute care clinic and additional hypothesis generating clinical questions.

653 DASATINIB AS A RAPID PHARMACOLOGICAL ON/OFF SWITCH FOR T CELL BISPECIFIC ANTIBODY-INDUCED T CELL ACTIVATION AND CYTOKINE RELEASE

1Gabrielle Leclercq*, 2Helene Haegel, 1Anneliese Schneider, 2Estelle Maurer Berger, 2Antje Walz, 2Christophe Boetsch, 1Vesna Pulko, 1Cristiano Ferlini, 1Christian Klein, 2Roche Innovation Center Zürich, Schlieren, Switzerland; 2Roche Innovation Center Basel, Basel, Switzerland

Background T cell bispecific antibodies (TCBs) are extremely potent T cell engagers, harboring a 2+1 format with one binder to the CD3ε chain and two binders to specific tumor antigens. Crosslinking of CD3 with tumor antigens triggers T cell activation, proliferation and cytokine release, leading to
tumor cell killing. TCB treatment is sometimes associated with safety liabilities due to on-target on-tumor, on-target off-tumor cytotoxic activity and cytokine release. Patients treated with TCBs may experience a Cytokine Release Syndrome (CRS), characterized by fever, hypotension and respiratory deficiency and associated with the release of pro-inflammatory cytokines such as IL-6, TNF-α, IFN-γ, and IL-1β. Off-tumor toxicity may occur if target antigens are expressed in healthy cells, which may potentially result in tissue damages and compromise the patient’s safety. Rapid pharmacological blockade of T cell activation and proliferation is a promising approach to mitigate these life-threatening toxicities. Tyrosine kinases such as SRC, LCK or ZAP70 are involved in downstream signaling pathways after engagement of the T cell receptor and blocking these kinases might serve to abrogate T cell activation when required. Dasatinib was identified as a potent candidate that switches off CAR T cell functionality.

Methods Using an in vitro model of target cell killing by human peripheral blood mononuclear cells, we assessed the reversible effects of dasatinib combined with CEA-TCB or HLA-A2-WT1-TCB on T cell activation and proliferation, target cell killing and cytokine release. At assay endpoints, T cell phenotype and target cell killing were measured by flow cytometry and supernatants were analyzed by Luminex to assess cytokine release. To determine the effective dose of dasatinib, the Incucyte system was used to follow kinetics of target cells killing by TCB in the presence of a dose response of dasatinib concentrations.

Results 100 nM dasatinib prevented TCB-mediated target cell killing when added in the system upon restimulation of activated T cells (figure 1). Dasatinib concentrations above 50 nM fully switched off target cell killing (figure 2) which was restored upon removal of dasatinib. These data confirm that dasatinib act as a potent and reversible on/off switch for activated T cells at pharmacologically relevant doses as they are applied in patients according to the label. 

Conclusions Taken together, we provide evidence for the use of dasatinib as a pharmacological on/off switch to mitigate off-tumor toxicities or CRS by T cell engaging therapies. These data are being validated in vivo. 

REFERENCES

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Abstract 653 Figure 2 Real time killing (Incucyte) of red fluorescent A375 cells loaded with RMF peptides by 10 nM HLA-A2 WT-1-TCB (left panel) and of red fluorescent MKN45 cells by 1 nM CEA-TCB (right panel) in the presence of different dasatinib concentrations ranging from 100 nM to 0 nM. Mean of technical duplicates + SEM

Abstract 653 Figure 1 Representative flow cytometry experiment reporting SKM-1 target cell viability upon first stimulation with 10 nM HLA-A2 WT-1-TCB in the absence of dasatinib (left panel) and upon second stimulation with 10 nM HLA-A2 WT-1-TCB in the presence of 100 nM dasatinib (right panel)

654 REAL WORLD INCIDENCE OF GRADE III AND HIGHER ADVERSE EFFECTS, EMERGENCY ROOM UTILIZATION AND HOSPITAL ADMISSIONS DURING TREATMENT WITH COMMONLY USED PD-1/PDL-1 TARGETING IMMUNE CHECK POINT INHIBITORS

1Nerea Lopetegui Liá, 2Syed Imran Jafri, 3Khalid Shalaby, 4Dimitrios Drekios, 5James Vedrenburgh, 1University of Connecticut, Hartford, CT, USA; 2University of Connecticut Health Center, Farmington, CT, USA; 3Smilow Cancer Hospital at St Francis Hos, Hartford, CT, USA

Background The landscape of cancer treatment has changed drastically since the development of Immune Checkpoint Inhibitors (ICI). ICIs have become the cornerstone to various cancer treatments. The adverse effect (AE) profile of ICI is different than conventional chemotherapy. Nivolumab and pembrolizumab target programmed cell death-1 T-cell receptor, whereas programmed death ligand-1 is targeted by atezolizumab and durvalumab. Easy tolerability and lack of myelo-suppression make immunotherapy an attractive treatment option. Some AEs can be severe, life-threatening, or even fatal (grade III and higher). Much of the data regarding AE profile is from clinical trials. The aim of our study is to review real world single institution AE data on the most commonly utilized ICIs.

Methods We reviewed a total of 229 patient charts who had received pembrolizumab, nivolumab, durvalumab or atezolizumab at Saint Francis Hospital in Hartford, CT, USA.