Experience of Immune-Related Adverse Events Associated with Ipilimumab and Nivolumab in a Single Center

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Background

Immune-related adverse events

- Immune checkpoint inhibitors have been approved for use in a many different cancers including metastatic melanoma, advanced non-small cell lung cancer, metastatic renal cell carcinoma, refractory Hodgkin's lymphoma, metastatic bladder cancer, advanced head and neck cancer and the list keeps growing each day.
- Screening for latent TB infection (LTBI) and treatment of patients with active disease has reduced reactivation rates. However, the risk of TB infection still remain high. The use of biologic therapy in patients with a lower risk of TB is a high priority.
- There is almost no prospective data on these toxicities and guidelines or recommendations are mostly based on symptomatic management from ongoing clinical trials.
- This study describes the clinical experience associated with ipilimumab and nivolumab in a Single Center in Johannesburg, South Africa.
- A retrospective, single center, non-interventional analysis was performed on data collected from the nivolumab and ipilimumab expanded access programme in South Africa (SA-EAP).
- The restropective study investigated toxicity and Immune-related adverse events (IrAE) associated with nivolumab and ipilimumab in patients with relapsed metastatic NSCLC, relapsed melanoma, relapsed Hodgkin's disease (HD) and relapsed renal cell carcinoma (RCC).

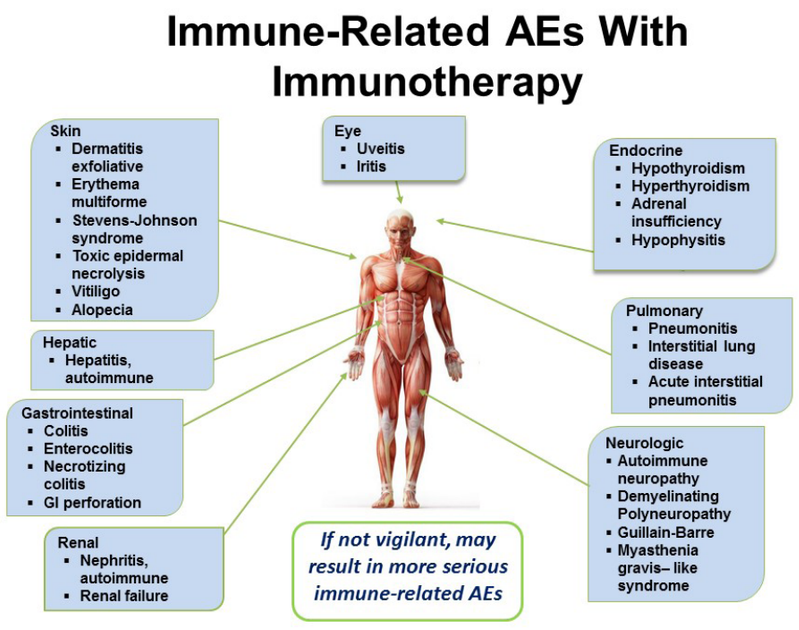

Figure 1. Immune-related AEs with immunotherapy.

Methods

Inclusion Criteria

NIVOLUMAB

NSCLC

- The patient has histologically- or cytologically-documented locally advanced squamous or non-squamous NSCLC.
- Patient has progressed on or after treatment with a minimum of 1 prior systemic treatment for stage IIIB or stage IV disease or with recurrent or progressive disease following multimodal therapy.

MALIGNANT MELANOMA

- The patient has previously treated unresectable stage III or stage IV melanoma and has progressed on or after treatment with an anti-CTLA-4 containing therapy.
- The patient has stable CNS metastases.
- In addition, patients must either be weaned off corticosteroids or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent).

RCC

- The patient has histologically confirmed advanced or metastatic RCC with a clear cell component.
- The patient has progressed on treatment or after treatment with a minimum of 1 prior line of therapy, including but not limited to sunitinib, pazopanib, axitinib, tivozanib, bevacizumab, mTOR inhibitors, in the advanced or metastatic setting.
- Prior cytokine therapy (e.g. IL-2, IFN-α), vaccine therapy or treatment of cytotoxics is allowed.

HD

- The patient is ineligible for or has received prior high-dose conditioning chemotherapy followed by ASCT, and must have received brentuximab vedotin* as a part of salvage therapy for cHL.
- The patient meets one of the following criteria according to the 2007 IWG criteria:
  - Documented absence of CR after 90 days from stem cell infusion for the most recent ASCT
  - Documented failure to achieve at least PR

Other Inclusion Criteria

- Aged ≥ 18 years of age.
- ECOG performance status of ≤ 2.
- All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue had resolved to Grade 1 (NCI CTCAE v4.0) or baseline.
- The patient had to sign informed consent.

IPILIMUMAB

Inclusion Criteria

- Histologically confirmed stage III (unresectable) or stage IV (metastatic) cutaneous, ocular or mucosal melanoma and patients with brain metastases should be asymptomatic.
- Failure or intolerance to at least 1 prior systemic treatment; aged ≥ 18 years of age.
- ECOG performance status of ≤ 2.

Exclusion Criteria

- Known, active or suspected autoimmune disease, HIV, Hepatitis B or C.
- Symptomatic brain metastases.
- Received other concurrent systemic anti-cancer treatments for melanoma.
- Other active, concurrent, malignant disease, with the exception of adequately treated basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix.
- Received other concurrent systemic anti-cancer treatments for NSCLC.
- Life expectancy of less than 6 weeks.
- The patient had previously participated in a nivolumab clinical study.
- The patient had received prior therapy with an anti-PD-1 or an anti-PD-L1 antibody.
- The patient had a condition requiring systemic treatment with either corticosteroids (> 10 mg/day prednisone equivalent) or other immunosuppressive medications within 14 days of administration of nivolumab.
- The patient had any known active chronic liver disease.
- The patient had previous malignancies, unless a complete remission was achieved at least 3 years prior to administration of nivolumab.
- The patient had a known medical condition (e.g. a condition associated with diarrhea or acute diverticulitis).
- The patient had not recovered from major surgery.
- The patient had a history of severe hypersensitivity reactions to other monoclonal antibodies.

Study Design

- Single center, retrospective study to evaluate the outcomes and toxicity of pretreated patients with NSCLC.
- Each patients signed informed consent and institutional ethics approval was obtained from the Human Sciences Research Council (HSRC) of South Africa.

Data Collection

- Data from different points in time throughout a patient's medical history were reviewed.
- The data included four aspects of treatment history: demographic features, disease characteristics, initial treatment at the time of enrollment in the SA-EAP and courses of treatment.
- Treatment-related information included history of concomitant drug use, details of nivolumab and ipilimumab treatment (date of first nivolumab or ipilimumab doses, number of infusions, and reason for discontinuation or omission).
- Adverse events reported by patients were routinely documented and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Statistical Analysis

- The analyses of data collected in this study will be mainly descriptive. All collected data and endpoint variables were summarised using descriptive statistics in addition to statistical modelling.

Results

- A total of 44 patients (28 males, 16 females) were analyzed.
- The median age was 63 years.
- The median PS was 1.

Nivolumab Group

- Metastatic melanoma 3 patients
- NSCLC: 18 patients
- RCC: 2 patients
- HD: 2 patients
- Nivolumab 167 cycles of n (median = 4, range 1 - 16)

Ipilimumab Group

- Metastatic melanoma 19 patients
- Ipilimumab 76 cycles (median = 4 cycles, range 1 - 4)

IrAE's

NIVOLUMAB

Seven IrAEs were documented out of 25 patients.

- Pneumonitis 2 patients.
- Skin rash 3 patients.
- Diarrhea 1 patient.
- Uveitis 1 patient.
- Autoimmune thrombocytopenia, nephritis 1 patient.
- Chest infection 3 patients (including pulmonary tuberculosis in a NSCLC patient).

IPILIMUMAB

Seven IrAEs were documented out of 15 patients.

- Endocrinopathy 3 patients (hypophysitis in 1 patient and hypothyroidism in 2 patients).
- Colitis Grade 3 or 4 reported in 3 patients (1 required infliximab).
- Hepatitis 1 patient.

No IrAE related deaths were documented.

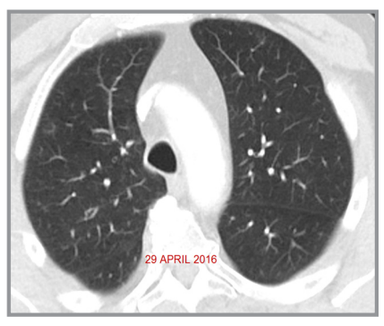

Figure 2. CT SCAN Pre-treatment.

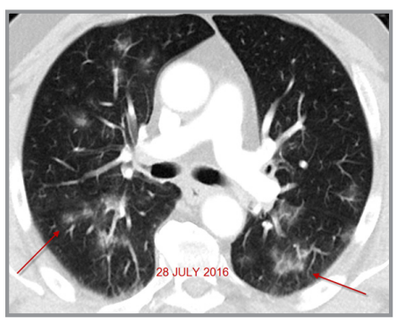

Figure 3. CT shown pneumonitis during nivolumab treatment.

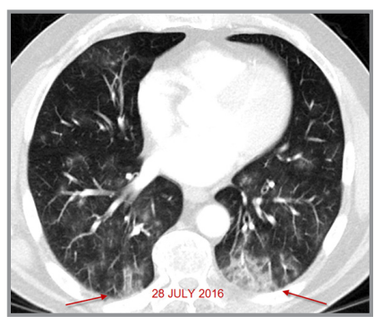

Figure 4. CT shown pneumonitis during nivolumab treatment.

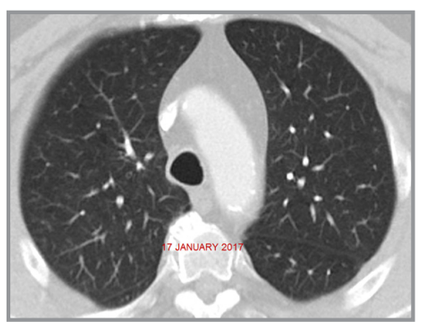

Figure 5. Post-treatment with corticosteroids and pneumonitis resolution.

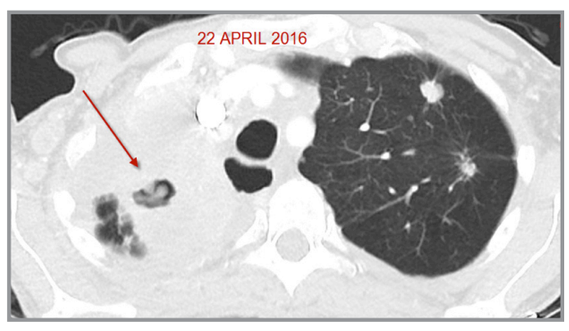

Figure 6. Complication of treatment: TB during nivolumab therapy.

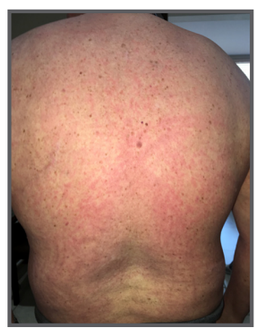

Figure 7. Skin rash.

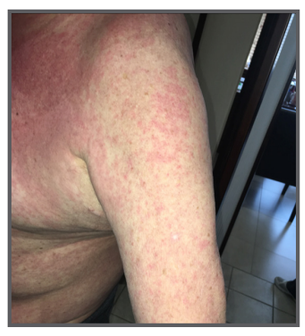

Figure 8. Skin rash.

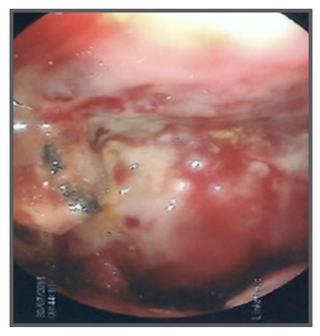

Figure 9. Severe Colitis.

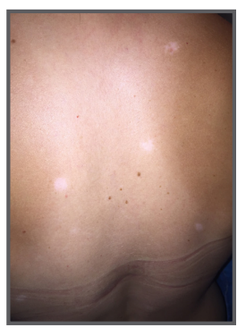

Figure 10. Vitiligo.

Conclusions

- A plethora of IrAEs are described with anti-PD1 and anti-CTLA-4 antibodies. Colitis was more common with ipilimumab while pneumonitis more common with nivolumab. Prompt diagnosis of IrAEs will result in decreased morbidity and mortality.

2017 MASCC/ISOO; June 22 - 24, 2017; Washington DC, United States