Patients with concurrent cancer and autoimmune disease:

Immu-NO-therapy?

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Learning Objectives

1. Describe immunotherapy and its place in oncology
2. Identify challenges with immunotherapy in patients with autoimmune disease
3. Evaluate the literature for the use of immunotherapy in autoimmune disease
4. Formulate an evidence-based recommendation regarding the use to immunotherapy in patients with pre-existing autoimmune diseases
1. **Cancer**1,2  
   a. Cancer is a group of more than 100 different diseases and is the second leading cause of death in Americans  
      i. Estimated new cases of cancer in 2019: 1,762,450  
      ii. Estimated deaths from cancer in 2019: 606,880  
   b. The mechanisms by which normal cells become cancer cells is incompletely understood  
      i. Believed that a physical, chemical or biological agent damages a normal cell leading to genetic alterations and modifications of mechanisms that control cell growth and proliferation  
      ii. Propagation of these alterations during cell division lead to unlimited growth, invasion and metastases

2. **The Immune System and Cancer**  
   a. Overview of the immune system3,4  
      i. The immune system defends the body using barriers, organs, cellular elements and molecules that interact with invading pathogens  
         1. Systems of Immunity:  
            a. Innate (native) immunity  
               i. Nonspecific to antigens and responds quickly after antigen exposure  
               ii. Includes physical components such as skin and mucous membranes as well as cellular components such as natural killer (NK) cells, dendritic cells, and macrophages (see figure 1)  
            b. Adaptive (acquired) immunity: Further divided into humoral and cellular immunity  
               i. Involves the formation of an immune response specific to the antigen  
               ii. Takes much longer to respond  
               iii. Includes CD8+ T cells, CD4+ T cells, and B cells (see figure 1)  

![Figure 1. Innate and Adaptive Immune responses](image)

b. **Cancer Immunoediting: Elimination, Equilibrium, Escape**5,6  
   i. Elimination  
      1. The Cancer-Immunity Cycle  
         a. The immune system has a protective role in tumor development  
         b. Adaptive and innate immunity destroy a developing tumor before the cancer becomes clinically apparent  
            i. Seven steps are associated with an anticancer immune response leading to effective killing of cancer cells (figure 2)
ii. Equilibrium
   1. If the cancer cell is not destroyed in the elimination phase, the equilibrium phase begins
   2. Adaptive immunity maintains cancer cells in a state of dormancy
      a. Activated CD4+ and CD8+ T-cells and pro-inflammatory cytokines
      b. Original variants of the cancer cell are destroyed
      c. New variants of the cancer cell are produced providing resistance to immune attack

iii. Escape
   1. Surviving tumor variants induce immunosuppressive effects within the tumor microenvironment and evade immune recognition
   2. The cancer cells expand in an uncontrolled manner leading to observable malignant disease

3. History of Cancer Immunotherapy
   a. Cancer Immunotherapy
      i. A form of cancer treatment that uses the power of the body’s own immune system to prevent, control and eliminate cancer
      1. Four types of immunotherapy:
         a. Non-specific immunotherapy: interleukin-2 (IL-2), interferon (IFN), and anti-tumor vaccines
         b. Oncolytic viruses
         c. Adoptive cell therapy: utilizes gene editing to modify a patient’s own immune cells
         d. Immune checkpoint inhibitors (ICI): monoclonal antibodies that enhance the function of anti-tumor T cells via the programmed cell death protein 1 (PD-1) pathway and the cytotoxic T lymphocyte associated protein 4 (CTLA-4) pathway

Figure 2. Interactions between tumor cells and the immune system

[Diagram of tumor cell interactions with the immune system]
ii. Cancer Immunotherapy Development Timeline

![Timeline Diagram]

Figure 3. Key developments in cancer immunotherapy and ICI history

4. Cancer Immunotherapy in Melanoma
   a. Melanoma
      i. Cancer that arises from melanocytes, or pigment producing cells, within the skin, the most serious type of skin cancer

![Figure 4: Stages of melanoma development]

Figure 4. Stages of melanoma development

   ii. Localized disease
      1. 84% of cases
      2. Treat with surgery for cure (5-year survival: 98.7%)

   iii. Metastatic disease
      1. 12% of cases
      2. Limited treatment options (5-year survival: 24.8%)

b. Treatment History of Metastatic Melanoma
   i. Dacarbazine
      1. Alkylating agent that was identified in the 1970s as a treatment option for melanoma
2. Adverse events: myelosuppression, hepatotoxicity, and nausea and vomiting
3. FDA approved based on disease response rate, never showed survival benefit
   a. Median overall survival 6-9 months
   b. 5-year overall survival was 6%

ii. High dose IL-2
   1. Human recombinant IL-2 promotes immune cell activation and response, works on the equilibrium component of immunoediting
   2. Adverse effects: hypotension, tachycardia, respiratory distress, altered mental status
      a. Requires ICU admission for administration due to likelihood of requiring pressor support
      b. Restricted to patients with excellent performance status
3. FDA approved based on improved overall survival
   a. Median survival of 11.4 months, with 20 patients still alive at 62 months and 15 alive past 4 years
   b. Unfortunately, only tolerated in a small number of patients

iii. Immune checkpoint inhibitors
   1. Ipilimumab
      a. Monoclonal antibody binding to CTLA-4, one mechanism tumors were using to induce immunosuppressive effects, the escape component of immunoediting
      b. Approved for use in 2011
      c. Hodi, et al (2010)\(^{21}\)
         i. Evaluated ipilimumab versus glycopeptide vaccine in 676 patients with unresectable stage III or IV melanoma, previously received dacarbazine, temozolomide, fotemustine, carboplatin, or IL-2
         ii. Median overall survival of 10.1 months with ipilimumab versus 6.4 months with other therapy
         iii. Excluded patient with pre-existing autoimmune disorders
   2. Nivolumab
      a. Monoclonal antibody binding to PD-1, one mechanism tumors use to induce immunosuppressive effects, the escape component of immunoediting
      b. CheckMate 066 (2015)\(^{22}\)
         i. Evaluated nivolumab versus dacarbazine in 418 patients with unresectable, previously untreated stage III or IV melanoma
         ii. Overall survival of 72.9% with nivolumab compared with 42.1% with dacarbazine
         iii. Excluded patients with autoimmune disorders
      c. CheckMate 067 (2015)\(^{18,19}\)
         i. Evaluated nivolumab versus nivolumab plus ipilimumab versus ipilimumab in 945 previously untreated patients with unresectable stage III or stage IV melanoma
         ii. 3-year overall survival evaluated in a subsequent analysis and was 58% with nivolumab-ipilimumab, 52% with nivolumab alone, and 34% with ipilimumab alone
         iii. Excluded patients with autoimmune disorders

c. National Comprehensive Cancer Network Cutaneous Melanoma Guidelines\(^{23}\)
   i. Metastatic or unresectable disease first line treatment regimens:
      1. Anti-PD-1 monotherapy: nivolumab or pembrolizumab
      2. Combination targeted therapy with BRAF V600-activating mutation
      3. Nivolumab + ipilimumab in certain patient populations
   ii. Dacarbazine and IL-2 no longer considered first line, preferred regimens
1. CTLA-4 \(^{24,25}\)

![Figure 5. CTLA-4 inhibition of T cells\(^{25}\)](image)

- How does CTLA-4 function normally in the immune system?
  - ii. CTLA-4 is expressed constitutively on regulatory T cells and plays a role in T cell activation in the lymph nodes (see figure 2a)
  - iii. CTLA-4 binds to B7 on antigen presenting cells, leading to decreased T cell activation and proliferation \(\rightarrow\) decreased immune response (see figure 2b)
  - iv. Blocking the action of CTLA-4 leads to a more robust immune activation (see figure 2c)
- e. Because CTLA-4 functions further upstream than PD-1 does, blocking the CTLA-4 pathway has more collateral effects than PD-1 inhibition

2. PD-1 and PD-L1\(^{5,10,26}\)

![Figure 6. PD-1/PD-L1 interactions in the immune system and with tumor cells\(^{26}\)](image)

- c. How does PD-1 function in the immune system normally?
  - i. PD-1 functions as an inhibitory signal within in the immune system to prevent overactivation (see figure 3)
  - ii. PD-1 expression is induced in a variety of activated immune cells and conditions, including:
    1. T cells that are constantly exposed to antigen
    2. Exhausted CD8 T cells
    3. Activated macrophages
4. Tumor microenvironment regulated by VEGF-A
   iii. PD-1 has two ligands, PD-L1 and PD-L2 that both serve to inhibit T cell function
      1. When PD-1 binds to PD-L1 T cells are inhibited
      2. Inversely, blocking either PD-1 or PD-L1, will prevent this inhibition
      3. See table 1 for cellular sites of PD-L1 and PD-L2 expression

d. Tumors express PD-L1 as a mechanism of inducing immunosuppression

<table>
<thead>
<tr>
<th>Table 1. Expression of PD-L1 and PD-L2$^{10}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PD-L1 Expression</strong></td>
</tr>
<tr>
<td>• Immune cells such as macrophages, B cells and dendritic cells and non-professional APCs</td>
</tr>
<tr>
<td>• Vascular endothelial cells</td>
</tr>
<tr>
<td>• Tumor/malignant cells and virus-infected cells</td>
</tr>
</tbody>
</table>

3. ICIs approved for use in oncologic conditions

<table>
<thead>
<tr>
<th>Table 2. Currently approved uses for ICIs$^{27-32}$</th>
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<tbody>
<tr>
<td><strong>Mechanism</strong></td>
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<tr>
<td><strong>FDA Approved Indications</strong></td>
</tr>
<tr>
<td>• Melanoma*</td>
</tr>
<tr>
<td>• Renal cell carcinoma**</td>
</tr>
<tr>
<td>• Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer</td>
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*Can be given as single agent
**Recommended first line treatment

4. ICI Adverse Effects$^{33-36}$
   a. Primary toxicity is related to over activation of the immune system against self, or immune related adverse events (irAE)
      ii. See table 3 for the most common manifestations of these irAEs
      iii. See figure 5 for a sample timeline of irAEs onset
<table>
<thead>
<tr>
<th>Description</th>
<th>Pneumonitis</th>
<th>Colitis/Diarrhea</th>
<th>Hepatitis</th>
<th>Dermatologic</th>
<th>Endocrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal or diffuse inflammation of the lung parenchyma</td>
<td>Inflammation of the colon including, abdominal pain, diarrhea and bloody stools</td>
<td>Elevation of AST/ALT, bilirubin. Rarely vomiting, jaundice</td>
<td>Rash, pruritis, vitiligo, erythematous macules, papules, and plaques</td>
<td>Thyroid dysfunction, adrenal insufficiency, hypophysitis</td>
<td></td>
</tr>
<tr>
<td>Agents</td>
<td>More common with PD-1, PD-L1</td>
<td>More common with CTLA-4</td>
<td>All</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>Incidence</td>
<td>Serious &lt;1% Overall ~4%</td>
<td>Serious up to 10% with CTLA-4</td>
<td>Overall 7-10%</td>
<td>Overall 14-17% Serious &lt;2%</td>
<td>Overall 1-2%</td>
</tr>
<tr>
<td>Timeline</td>
<td>Median onset 2.8 months (range 9 days to 19.2 months)</td>
<td>6-8 weeks after initiation of ipilimumab less predictable with PD-1/PD-L1</td>
<td>8-12 weeks after initiation of ipilimumab less predictable with PD-1/PD-L1</td>
<td>Within one month but can occasionally arise later in therapy</td>
<td>8-12 weeks after initiation</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Cough, dyspnea, CT chest</td>
<td>Clinical Rule out other causes</td>
<td>Lab values Rule out other causes</td>
<td>Clinical Rule out other causes</td>
<td>Lab values (TSH, hormone levels, etc.)</td>
</tr>
<tr>
<td>Management</td>
<td>Grade 1: Consider holding ICI</td>
<td>Grade 1: Consider holding ICI, loperamide</td>
<td>Grade 1: Continue ICI</td>
<td>Grade 1: Continue ICI; topical steroids and emollients or oral antihistamines</td>
<td>Figure 7. Onset of irAEs with Ipilimumab³³³⁷</td>
</tr>
<tr>
<td></td>
<td>Grade 2: Hold ICI, consider, prednisone 1-2mg/kg/day</td>
<td>Grade 2: Hold ICI, prednisone 0.5-1mg/kg/day</td>
<td>Grade 2: Hold ICI, consider prednisone 0.5-1mg/kg/day</td>
<td>Grade 2: Consider holding ICI, same treatment as grade 1 OR consider prednisone 0.5-1mg/kg/day</td>
<td>Elevated TSH: -Continue ICI, levthyroxine</td>
</tr>
<tr>
<td></td>
<td>Grade 3-4: Discontinue ICI, prednisone 1-2mg/kg; can add infliximab or mycophenolate</td>
<td>Grade 3-4: Discontinue ICI, IV methylprednisolone 2mg/kg/day; can add infliximab or vedolizumab</td>
<td>Grade 3-4: Discontinue ICI, prednisone 1-2mg/kg/day; can, add mycophenolate</td>
<td>Grade 3 or 4: Hold ICI, topical steroids and prednisone 1-2mg/kg/day</td>
<td>Hypophysitis: -Hold ICI until symptoms resolve, if symptomatic treat with prednisone 1-2mg/kg/day</td>
</tr>
</tbody>
</table>

**Figure 7.** Onset of irAEs with Ipilimumab³³³⁷
b. Several studies have shown a correlation between the development of irAEs and ICI response
   iv. Grangeon, et al (2019)\textsuperscript{34}
      1. Evaluated 270 patients with NSCLC treated with nivolumab
      2. Median progression free survival 5.2 months in patients with irAEs of any grade and 1.97 months in patients without irAEs
      3. Median overall survival 8.21 months in patients without irAEs and was not reached at study conclusion in patients with irAEs

c. Management\textsuperscript{33,35,36}
   i. Depends on manifestation and severity of the side effect
   ii. Most severe adverse effects are treated with systemic or topical corticosteroids to suppress the overactive immune response
      1. See table 3 for management of individual manifestations of irAEs
      2. See appendix A for toxicity grading
   iii. Corticosteroids (prednisone doses $\geq$ 10 mg or equivalent) should be avoided with immunotherapy as they directly antagonize the immune system
      1. Arbour, et al. (2018)\textsuperscript{38} evaluated patients receiving PD-1 inhibitors and compared those receiving corticosteroids of $\geq$10mg of prednisone equivalent at baseline to those who did not
      2. Patients receiving baseline corticosteroids had poorer outcomes than those who were not, including significantly shorter progression free survival and overall survival

Cancer and Autoimmune Disorders

1. Autoimmune disease background\textsuperscript{39-41}
   a. Autoimmune disorders affect 3-5% of the population
   b. There are at least 100 distinct autoimmune disorders that have been described, some are organ specific and others are known to affect many different organ systems
      i. Significantly lower survival in patients with pre-existing autoimmune disorders
      ii. See figure 2 for autoimmune disorders by organ system
   c. The development of all autoimmune disorders is not necessarily the same, but all are considered an intolerance to self by the immune system

![Figure 8. Autoimmune disorders can affect a wide variety of organ systems]\textsuperscript{39}
2. Link between autoimmune disorders and cancer\textsuperscript{39,41,42}
   a. Many autoimmune disorders, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and inflammatory bowel disease (IBD), are associated with an increased risk of developing cancers
   b. Constant immune stimulation and chronic inflammation seen with autoimmune disorders is thought to put patients with autoimmune disorders at higher risk of developing cancer

3. Autoimmunity and the PD-1 pathway\textsuperscript{42,43}
   a. Recent evidence has shown dysregulation in the PD-1/PD-L1 pathway among several autoimmune disorders
   b. Other autoimmune disorders have some evidence for PD-1 involvement including autoimmune hepatitis, Behcet’s disease, myasthenia gravis, autoimmune uveitis, Sjogren’s syndrome, systemic lupus erythematosus (SLE), Ankylosing spondylitis, and myocarditis

**Clinical Question**

Can immune checkpoint inhibitors be used in patients with pre-existing autoimmune disease?

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>Design and Methods</strong></td>
<td>Retrospective chart review across 13 melanoma centers in the US, Australia, and Europe to explore the safety and efficacy of anti-PD-1 antibodies in patients preexisting autoimmune disorders</td>
<td></td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td><strong>Inclusion Criteria</strong></td>
<td><strong>Exclusion Criteria</strong></td>
</tr>
<tr>
<td></td>
<td>Advanced melanoma</td>
<td>Any patients not meeting inclusion criteria</td>
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<tr>
<td></td>
<td>Pre-existing autoimmune disorders and/or major immune related adverse effects with prior ipilimumab</td>
<td></td>
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<tr>
<td></td>
<td>Treated with anti-PD-1 antibodies</td>
<td></td>
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<tr>
<td><strong>Factors evaluated</strong></td>
<td>Patient characteristics (e.g. age, sex, prognostic factors, pathologic staging)</td>
<td></td>
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<tr>
<td></td>
<td>Activity or inactivity of autoimmune disorder defined by clinician on clinical grounds</td>
<td></td>
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<tr>
<td></td>
<td>Immunosuppressive therapy for autoimmune disorder at time of anti-PD-1 initiation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adverse effects classified by Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 grading</td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Safety of anti-PD-1 antibodies, defined by worsening of the autoimmune disorder or recurrent of prior irAE with ipilimumab necessitating therapeutic intervention with systemic immune-modifying agents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Incidence of irAEs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment response:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o Response evaluation criteria in solid tumors (RECIST) 1.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o Progression-free survival (PFS)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o Duration of response</td>
<td></td>
</tr>
<tr>
<td></td>
<td>o Overall survival (OS)</td>
<td></td>
</tr>
</tbody>
</table>
Statistical Analysis

- Categorical and continuous variables were summarized using percentages and medians, no formal hypothesis testing performed
- PFS and OS estimated using Kaplan-Meier method

Results

Baseline characteristics

N=119, 109 receiving pembrolizumab and 10 receiving nivolumab
Preexisting autoimmune disorder (N=52), significant ipilimumab toxicity (N=67)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>71 (23-88)</td>
</tr>
<tr>
<td>Autoimmune disorder</td>
<td></td>
</tr>
<tr>
<td>Rheumatologic</td>
<td>27 (52%)</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>8 (15%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Neurologic</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Active autoimmune disorder at PD-1 start</td>
<td>15 (29%)</td>
</tr>
</tbody>
</table>

Treatment of autoimmune disorder at PD-1 Start

<table>
<thead>
<tr>
<th>Treatment of autoimmune disorder at PD-1 Start</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>32 (62%)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>9 (17%)</td>
</tr>
<tr>
<td>Steroid-sparing agents</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Both steroids and steroid-sparing agents</td>
<td>5 (10%)</td>
</tr>
</tbody>
</table>

Outcomes

- 20 patients (38%) experienced a flare of their underlying autoimmune
  - 14/27 (52%) of patients with rheumatologic disorders
  - 3/8 (37.5%) with psoriasis
  - No flares occurred in patients with gastrointestinal, neurologic, or respiratory disorders
- Flare severity
  - Most flares (85%) were mild, grade 1-2
  - 8 patients interrupted therapy and 2 permanently discontinued
- Flares occurred at a median 38 days after therapy initiation
- More flares in those with active symptoms at therapy initiation than with inactive (9/15 vs 11/37, P=0.039)
- Conventional adverse events occurred in 15 patients, 5 of which were grade 3-4
- Treatment response observed in 17/52 (33%) of patients
- Response rates were similar in those with and without flares of autoimmune disorders
- Median progression free survival (PFS)- 6.2 months
- 14 patients died during study period

Author’s conclusions

Anti-PD-1 antibodies induce relatively frequent immune toxicities in patients with baseline autoimmune, but these immune toxicities are often mild and easily managed, and the patients achieve high rates of clinical response

Reviewer’s Critique

Strength’s

- Wide inclusion criteria

Limitations

- Retrospective
- Limited statistical analysis performed
- Small patient population, particularly small representation of certain autoimmune disorders
- Baseline autoimmune therapy not provided
Overall Conclusions

- Overall rates of immune-related adverse effects were low and most were not serious
- Largest autoimmune populations were rheumatological, dermatological, and gastrointestinal
- Overall patient populations in this study were too small to make broad conclusions about the use of immunotherapy in this patient population, but in general, a co-occurring autoimmune disorder should not solely eliminate immunotherapy as a therapeutic option.


<table>
<thead>
<tr>
<th>Design and Methods</th>
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<tbody>
<tr>
<td>Prospective, observational cohort study to describe and analyze the safety and effectiveness of anti-PD-1 antibodies in patients with pre-existing autoimmune disorder</td>
</tr>
</tbody>
</table>

### Population

- Patients included in the prospective Registry of Severe Adverse Events of Immunomodulating Monoclonal Antibodies in Oncology (REISAMIC) registry
- Registry includes all patients treated with anti-PD-1 antibodies following marketing authorization as part of patient access programs for unlicensed medication or during compassionate use

### Inclusion criteria:

- Malignant hematologic disease
- A second advanced cancer
- Chronic viral infection
- Autoimmune disorders not included: atopic diseases, metabolic inflammatory diseases, and autoimmunity caused by infectious diseases or drugs

### Factors evaluated

- Patient characteristics (e.g. age, sex, pathologic staging)
- Pre-existing autoimmune disorder and treatment of autoimmune disorder
- Patients cancer status
- Previous cancer treatments

### Outcomes

- Overall survival
- Overall response rate
- Toxicity including immune related adverse events
- Discontinuation or maintenance of therapy

### Statistical Analysis

- Categorical variables described as number and percentage
- Continuous variables were described as the number, mean with standard deviation, and median interquartile range
- IrAE-free survival and OS in the two groups were estimated using the Kaplan Meier method and compared using a log-rank test
- A univariate logistic regression was used for intergroup comparisons of the ORR

### Results

#### Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre-existing autoimmune disorder (n=45)</th>
<th>Autoimmune-Free (n=352)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, median (IQR), years</td>
<td>62.3 (23-88)</td>
<td>62.4 (20-92)</td>
</tr>
<tr>
<td>Pre-existing autoimmune disorder, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatologic</td>
<td>33</td>
<td>--</td>
</tr>
<tr>
<td>Endocrine</td>
<td>9</td>
<td>--</td>
</tr>
<tr>
<td>Rheumatological</td>
<td>7</td>
<td>--</td>
</tr>
<tr>
<td>Symptomatic autoimmune disorder, n (%)</td>
<td>25 (55.6%)</td>
<td>--</td>
</tr>
<tr>
<td>Cancer type, n (%)</td>
<td></td>
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</tbody>
</table>

N=45 patients enrolled in REISAMIC compared with 352 autoimmune disorder-free patients over the same period
<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Cancer Stage, n (%)</th>
<th>Immunotherapy received, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>III 3 (6.7%)</td>
<td>Anti-PD-1 agents 44 (97.8%)</td>
</tr>
<tr>
<td></td>
<td>IV 42 (93.3%)</td>
<td>Anti-PD-L1 agent 1 (2.2%)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>III 3 (6.7%)</td>
<td>Anti-PD-1 agents 215 (61.1%)</td>
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<tr>
<td></td>
<td>IV 133 (37.8%)</td>
<td>Anti-PD-L1 agent 0</td>
</tr>
<tr>
<td>Other</td>
<td>III 3 (6.7%)</td>
<td>Anti-PD-1 agents 4 (1.1%)</td>
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<td></td>
<td>IV 304 (86.4%)</td>
<td>Anti-PD-L1 agent 0</td>
</tr>
</tbody>
</table>

Outcomes

Immune related adverse events (irAEs) in patients with autoimmune disorders:

- 20/45 patients experienced irAEs (44.4%) (grade 2-14, grade 3-5, no grade 4 or 5 events)
  - 11/20 events were considered a flare
  - 10 patients developed symptoms that were not associated with pre-existing autoimmunity (thyroiditis, colitis, gastritis, etc.)
- 15/20 patients continued therapy despite AEs
- 12/20 patients required a specific treatment for irAE (6 being systemic corticosteroids)
- 4 patients required definitively discontinuation of therapy due to colitis, acute tubulointerstitial nephritis (ATN), and a flare of myasthenia gravis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre-existing autoimmune disorder (n=45)</th>
<th>Autoimmune-free (n=352)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>irAE</td>
<td>20/45 (44.4%)</td>
<td>102/352 (29%)</td>
<td>--</td>
</tr>
<tr>
<td>irAE-free survival time, median</td>
<td>5.4 months</td>
<td>13 months</td>
<td>0.0002</td>
</tr>
<tr>
<td>Overall survival at last follow-up</td>
<td>26 (57.8%)</td>
<td>Not provided</td>
<td>0.38</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>38%</td>
<td>28%</td>
<td>0.098</td>
</tr>
</tbody>
</table>

Author's conclusions

Patients with pre-existing autoimmune disorders had an increased risk of irAEs and experiencing flares when treated with anti-PD-1 antibodies. However, these agents seem to be just as safe and effective in patients with autoimmune disorders

Reviewer's Critique

Strengths

- Prospective

Limitations

- Small overall autoimmune disorder patient population
- Observational

Overall Conclusions

- Patients with pre-existing autoimmune disorders experienced more irAEs but these tended to be non-severe and did not generally affect the patient’s ability to stay on the therapy
- Overall response rates and overall survival in the autoimmune disorder population were comparable to autoimmune-free patients
- Largest autoimmune populations included were dermatologic, endocrine, and rheumatologic


Design and Methods

Systematic review to describe the use of checkpoint inhibitors in patients with cancer and pre-existing autoimmune disease

<table>
<thead>
<tr>
<th>Population</th>
<th>Inclusion Criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case reports, case series, and observational</td>
<td>Diagnosis of an autoimmune disorder after immunotherapy</td>
</tr>
</tbody>
</table>
• Patients of any age with cancer and an established diagnosis of an autoimmune disease before receiving a checkpoint inhibitor
• Provided a detailed clinical description of each case
• Developed an adverse event and demonstrated autoimmune-specific autoantibodies after the receipt of immunotherapy

Factors evaluated
• Patient demographic and baseline characteristics
• Status of pre-existing autoimmune disease – active versus inactive and presence of immunosuppressive therapy
• ICI agent patient is receiving
• Treatment related adverse events, time to development of event, and management of event
• Clinical outcomes including adverse event outcomes
• Tumor response

Outcomes
• Adverse events both new irAEs and exacerbations of autoimmune disorder
• Results were stratified by immunotherapy used, pre-existing autoimmune disorder, activity of pre-existing autoimmune disorder, and autoimmune disorder actively being treated

Statistical Analysis
• Descriptive statistics with medians and ranges for continuous variables and frequencies and percentages for dichotomous variables

Results
Baseline characteristics
49 publications included: 39 case reports, 4 case series, and 5 retrospective observational studies
N=123 patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>61.4 (26-87)</td>
</tr>
<tr>
<td>Cancer, n (%)</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>103 (83.7)</td>
</tr>
<tr>
<td>Lung</td>
<td>16 (13)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>Autoimmune disorder, n (%)</td>
<td></td>
</tr>
<tr>
<td>Psoriasis or psoriatic arthritis</td>
<td>28 (22.8)</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>20 (16.3)</td>
</tr>
<tr>
<td>Autoimmune thyroid disease</td>
<td>11 (8.9)</td>
</tr>
<tr>
<td>Ulcerative colitis or Crohn’s Disease</td>
<td>13 (10.6)</td>
</tr>
<tr>
<td>Other</td>
<td>51 (41.4)</td>
</tr>
<tr>
<td>Active autoimmune disorder, %</td>
<td>46.2%</td>
</tr>
<tr>
<td>Currently receiving therapy for autoimmune disorder at initiation of immunotherapy, %</td>
<td>43.6%</td>
</tr>
<tr>
<td>Immunotherapy received, n (%)</td>
<td></td>
</tr>
<tr>
<td>Anti-PD-1 Agent</td>
<td>64 (52.0)</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>55 (44.7)</td>
</tr>
<tr>
<td>Anti-PD-L1 Agent</td>
<td>1 (0.8)</td>
</tr>
</tbody>
</table>

Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Psoriasis/Psoriatic Arthritis (n=28)</th>
<th>Rheumatoid Arthritis (n=20)</th>
<th>Autoimmune thyroid disease (n=11)</th>
<th>Inflammatory Bowel Disease (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events, n (%)</td>
<td>25 (89)</td>
<td>15 (75)</td>
<td>5 (45)</td>
<td>8 (62)</td>
</tr>
<tr>
<td>Recurring or worsening</td>
<td>18 (64)</td>
<td>7 (35)</td>
<td>2 (17)</td>
<td>5 (39)</td>
</tr>
<tr>
<td>New irAEs</td>
<td>3 (11)</td>
<td>5 (25)</td>
<td>3 (27)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Both new and recurring</td>
<td>4 (14)</td>
<td>3 (15)</td>
<td>--</td>
<td>1 (8)</td>
</tr>
</tbody>
</table>
• No differences observed between patients with active autoimmune disorders versus inactive
• Patients receiving therapy for autoimmune disorders at initiation of immunotherapy had fewer adverse events compared with those not receiving therapy (59% vs 83%)
• More disease flares with anti-PD-1/anti-PD-L1 agents (62% vs 36%)
• More new-onset irAEs with ipilimumab (42% vs 26%)
• Adverse events improved in 90% of patients
• 25 (50%) of patients with adverse events had a partial or complete response with their cancer compared with 5 patients (35.7%) who did not have adverse events
• 5 patients died, 2 of which were due to a serious adverse event

Author's conclusions
Flares and irAEs are not uncommon in patients with autoimmune disorders and they may be successfully managed without discontinuation of therapy. However, they may occasionally result in severe, fatal disease and clinicians should be aware that patients should be monitored closely. The severity of the patients underlying autoimmunity, cancer prognosis, and alternative therapeutic options should all be weighed as risks and benefits

Reviewer's Critique

Strength’s
- Provided outcomes broken down by autoimmune disorder, autoimmune therapy and autoimmune control

Limitations
- Lack of consistent definitions and pertinent data of included studies
- No statistical analyses performed
- Most data from case reports, will tend to be more unique/ unusual and less representative of the population

Overall Conclusions
- The nature of studies included in this systematic review makes it difficult to draw specific conclusions about the use of immunotherapy in patients with pre-existing autoimmune disorders
- This study provides some evidence by specific autoimmune disorder types across several different cancers
- Largest autoimmune populations included were dermatologic, rheumatologic, and thyroid


Design and Methods
Retrospective, multicenter observational study of patients with pre-existing autoimmune disorders and advanced cancer treated with anti-PD-1 agents at 15 Italian centers from September 2013 through May 2018, for safety and efficacy

Population

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with stage IV cancers</td>
<td>None</td>
</tr>
<tr>
<td>Treated with single agent anti-PD-1 agents, regardless of treatment line</td>
<td></td>
</tr>
</tbody>
</table>
Factors evaluated
• Patient characteristics (e.g. age, sex, ECOG score, disease burden, treatment line)
• Disease responses as evaluated by RECIST criteria
• Pre-existing autoimmune disorder categorized by organ system
• Activity of autoimmune disorder at initiation of immunotherapy and concomitant autoimmune therapy
• Immune related adverse events

Outcomes
• Incidence of autoimmune disorders among patients with cancer undergoing immunotherapy with anti-PD-1
• Incidence of irAEs between patients with and without pre-existing autoimmune disorders and inactive versus active autoimmune disorders
• Evaluate the correlation between pre-existing autoimmune disorders and clinical outcomes:
  o Objective response rate (ORR)
  o Median progression free survival (PFS)
  o Median overall survival (OS)

Statistical Analysis
• χ² and Fisher’s exact test were used to evaluate ORRs, the incidence of irAEs and the discontinuation rates due to adverse events among subgroups, according to the sample size
• Odds ratios (ORs) with 95% confidence intervals (95% CIs) were used to estimate the association between the incidence of irAEs and covariates
• In the multivariate analysis, logistic regression was used to evaluate the parameters that were significant at the univariate safety analysis (primary tumor was included in multivariate analysis regardless of its significance at univariate analysis)
• Median PFS, median OS, median time to irAEs, and median follow-up were evaluated using the Kaplan-Meier method
• Cox proportional hazards model was used to evaluate predictor variables in univariate and multivariate analysis for median PFS and median OS

Results

Baseline characteristics
N=751 patients, 85 of which has preexisting autoimmune disorders

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population</td>
<td></td>
</tr>
<tr>
<td>Median Age, years</td>
<td>69</td>
</tr>
<tr>
<td>Cancer type</td>
<td></td>
</tr>
<tr>
<td>NSCLC</td>
<td>492 (65.5)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>159 (21.2)</td>
</tr>
<tr>
<td>RCC</td>
<td>94 (12.5)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (0.8)</td>
</tr>
<tr>
<td>Pre-existing autoimmune disorders</td>
<td></td>
</tr>
<tr>
<td>Active Disease</td>
<td>15 (17.6)</td>
</tr>
<tr>
<td>Type of Disease</td>
<td></td>
</tr>
<tr>
<td>Thyroid disorders</td>
<td>51 (60)</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>14 (16.4)</td>
</tr>
<tr>
<td>Rheumatologic</td>
<td>10 (11.8)</td>
</tr>
<tr>
<td>Other or multiple sites</td>
<td>11 (12.9)</td>
</tr>
<tr>
<td>On autoimmune treatment</td>
<td>15 (17.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No autoimmune disorder (n=666)</th>
<th>Inactive autoimmune disorders (n=70)</th>
<th>Active autoimmune disorders (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>irAE, any grade, n (%)</td>
<td>266 (39.9, 95% CI: 35.2-45.0)</td>
<td>45 (64.3, 95% CI: 46.8-86.0)</td>
<td>11 (73.3, 95% CI: 44.9-92.2)</td>
</tr>
<tr>
<td>irAE, grade 3 or 4, n (%)</td>
<td>59 (8.8, 95% CI: 6.7-11.4)</td>
<td>6 (8.6, 95% CI: 3.1-18.6)</td>
<td>2 (13.3, 95% CI: 1.6-48.1)</td>
</tr>
</tbody>
</table>
Incidence of overall irAEs was significantly higher in patients with pre-existing autoimmune disorders, as compared with patients without (65.9% vs 39.9%, p<0.0001)

No significant differences in the rates of serious (grade 3-4) irAEs (9.4% vs 8.8%, p=0.8663)

At multivariate analysis, pre-existing autoimmune disorders (both inactive and active), female sex, and ECOG-PS 0-1 were all significantly related to greater incidence of irAEs of any grade

No significant differences in patients discontinuing treatment

Most common overall adverse events were dermatologic, endocrine, and gastrointestinal

Most common grade 3-4 adverse events were gastrointestinal, skin, and pneumological

Primary tumor (melanoma), first line treatment, low burden of disease, and ECOG 0-1 were found to be independent predictors of increased PFS

Author’s conclusions

Patients with pre-existing autoimmune disorders who underwent treatment with anti-PD-1 agents have a statistically significant increase in the risk of irAEs as well as risk of worsening of their underlying autoimmune disorder. However, this does not mean that these patients should not be treated with these agents; these agents should be evaluated for each individual patient

Reviewer’s Critique

Strengths

- Data stratified by presence of autoimmunity and activity of autoimmune disorder

Limitations

- Retrospective
- Baseline characteristics not stratified by autoimmunity
- Small autoimmune disorder sample sizes
- Baseline steroid doses not provided

Overall Conclusions

- Patients with pre-existing autoimmune disorders have an increased risk of overall irAEs and flares of their underlying autoimmune disorder, but not severe irAEs
- Patients with autoimmune disorders demonstrated benefit with ICI therapy with treatment response and overall survival
- Largest autoimmune populations included were thyroid, dermatologic, and rheumatologic

Conclusions and Recommendations

1. Immunotherapy, immune checkpoint inhibitors specifically, have represented a landmark improvement in cancer treatment and play a key role in many different cancers
2. Patient’s with autoimmune disorders were excluded from these landmark studies
3. Immune related adverse effects are the most common side effects with immunotherapy and patients with pre-existing autoimmune disorders are at increased risk for developing irAEs
4. Rates of serious adverse events in this population remain similar to those seen in patients without autoimmune disorders
5. Patient’s with pre-existing autoimmune disorders may still benefit from immunotherapy and should be considered for immunotherapy even with an increased risk of irAEs.
6. Considerations for any patient with concurrent autoimmunity and cancer
   a. Standard of care for cancer type and the number of first-line treatment options:
      i. NSCLC: Multiple first line treatment options with and without immunotherapy
      ii. Metastatic melanoma: Immunotherapy is standard of care
b. Type of autoimmune disorder:
   i. Dermatologic, rheumatologic, and thyroid autoimmune disorders have the most data with ICIs
   ii. Autoimmune disorders that can be easily monitored and adjusted and/or is not typically a
       progressive condition: thyroid disorders and type 1 diabetes mellitus
   iii. Neurologic conditions, including multiple sclerosis and myasthenia gravis, and
       severe/uncontrolled gastrointestinal disorders do not have enough data to make firm
       recommendations with ICI use

c. Current autoimmune disorder therapy:
   i. Data does not specify which autoimmune treatment patients were receiving while on
      concurrent ICIs
   ii. Patients receiving no treatment, topical therapies, thyroid replacement and low dose
      corticosteroids (≤ prednisone 10mg daily or equivalent) should not have interaction between
      autoimmune disorder treatment and ICI therapy
   iii. Patients receiving systemic corticosteroids (>10mg prednisone daily or equivalent), other
      systemic immunosuppressive therapies and newer biologic agents may have interaction
      between autoimmune treatment and ICI therapy

d. Current autoimmune disorder control:
   i. Data eludes that patients with pre-existing autoimmune disorders have an increased risk of
      overall irAEs and flares of their underlying autoimmune disorders whether well controlled or not
      well controlled
   ii. Patients with dermatologic, rheumatologic and thyroid disorders receiving concurrent ICIs had
      flares or irAEs that were not severe regardless of autoimmune disorder control prior to ICI
      initiation

e. Final recommendations:
   i. For patients with cancers in which immunotherapy is the standard of care and a concurrent
      dermatologic, rheumatologic or thyroid autoimmune disorder, we have sufficient evidence for
      the safety of ICI use in this population
   ii. To limit interactions between autoimmune disorder therapy and ICI, it is preferred that patients
      are receiving no treatment, topical therapies, thyroid replacement and low dose corticosteroids
      (≤ prednisone 10mg daily or equivalent) for their dermatologic, rheumatologic or thyroid
      disorder when being initiated on an ICI
   iii. For patients who do not meet these criteria, consideration for treatment with immunotherapy
      should be reviewed on a case by case basis

References

29. Keytruda (pembrolizumab) [prescribing information]. Whitehouse Station, NJ: Merck & Co Inc; April 2019
31. Imfinzi (durvalumab) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; February 2018.

Appendices

Appendix A. irAE Grading by System

<table>
<thead>
<tr>
<th>Pneumonitis</th>
<th>Colitis/Diarrhea</th>
<th>Hepatitis*</th>
<th>Dermatologic</th>
<th>Endocrine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong></td>
<td>Asymptomatic; confined to one lobe of the lung or &lt;25% of lung parenchyma; clinic or diagnosis observations only</td>
<td>Fewer than 4 bowel movements above baseline per day and no colitis symptoms</td>
<td>Alanine transaminase (ALT) or aspartate transaminase (AST) &lt;3x ULN</td>
<td>Macules/papules covering &lt;10% body surface area (BSA) with or without symptoms -OR- mild/localized pruritis</td>
</tr>
<tr>
<td><strong>Grade 2</strong></td>
<td>Presence of new/worsening symptoms including: shortness of breath, cough, chest pain, fever, and increased oxygen requirement</td>
<td>4-6 bowel movements above baseline per day, colitis symptoms, not interfering with ADLs</td>
<td>AST, ALT 3-5x ULN</td>
<td>Macules/papules covering 10-30% BSA, with or without symptoms, limiting instrumental activities of daily living (iADLs) - OR- intense or widespread intermittent pruritis</td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td>Severe symptoms involving all lung lobes or &gt;50% of lung parenchyma, limiting self-care ADLs</td>
<td>More than 6 bowel movements above baseline per day, colitis symptoms, interfering with ADLs, hemodynamic instability, hospitalization, other serious complications</td>
<td>AST, ALT &gt;5-20 x ULN</td>
<td>Macules/papules covering &gt;30% BSA with or without symptoms, limiting self-care activities of daily living (ADLs) - OR- intense, widespread, constant pruritis</td>
</tr>
<tr>
<td><strong>Grade 4</strong></td>
<td>Life threatening respiratory compromise</td>
<td></td>
<td>AST, ALT &gt;20x ULN</td>
<td></td>
</tr>
</tbody>
</table>

*For Grade >1 transaminitis with bilirubin >1.5x ULN (unless Gilbert’s syndrome), rule out viral etiology, disease related hepatic dysfunction, other drug-induced transaminase elevations, consider GI evaluation and limit/discontinue hepatotoxic medications.