ENDOCRINE ADVERSE EVENTS ASSOCIATED WITH CHECKPOINT IMMUNOTHERAPY

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Immune checkpoint inhibitors in the news this year

The New York Times

Immune System, Unleashed by Cancer Therapies, Can Attack Organs

Cell Wars: The Science of Immunotherapy

Background

- In recent years, immune checkpoint inhibitors have emerged as effective therapies for advanced neoplasias

- These aim to improve the ability to immunologically reject the tumor by generating an adequate immune response and breaking tumor-induced immune tolerance

- Immune regulatory monoclonal antibodies developed have focused on inhibiting various checkpoints:
  - *Cytotoxic T lymphocyte antigen 4 receptor (CTLA-4)*
  - *Programmed death -1 (PD-1) receptor pathway*

Background

2011
- Ipilimumab (anti-CTLA4 Ab) approved for treatment of metastatic melanoma

2013
- Science Magazine named cancer immunotherapy “the breakthrough of the year”

2014 2015
- Nivolumab and pembrolizumab (anti-PD1) approved for melanoma, RCC, and NSCLC
- Tremelimumab (anti-CTLA4 Ab) received FDA approval for malignant mesothelioma

2016
- Atezolizumab (anti-PD-L1 Ab) received FDA approval for treatment of metastatic NSCLC

2017
- Durvalumab (anti-PD-L1 Ab) and Pidilizumab (anti-PD-1 Ab) are in clinical trials

Background

- Immune checkpoint inhibitors have many indications thus far:
  - *Metastatic melanoma*
  - *Metastatic non-small cell lung cancer*
  - *Advanced renal cell carcinoma*
  - *Classical Hodgkin lymphoma that has relapsed or progressed after stem cell transplantation*
  - *Metastatic squamous cell carcinoma of the head and neck*
  - *Malignant mesothelioma*
- Anti-CTLA4 and anti-PD1 Ab have different mechanisms of action, but allow for increased T cell activation, proliferation, and activity

Background

- In contrast to conventional chemotherapy, boosting the immune system leads to a unique constellation of inflammatory toxicities known as immune-related adverse events (irAEs)

- Recognition and management of irAEs is crucial to be able to use these agents
  - *While most irAEs are mild, some can be life-threatening*

- Use of these agents is set to increase due to their dramatic impact on survival in a variety of advanced staged cancers

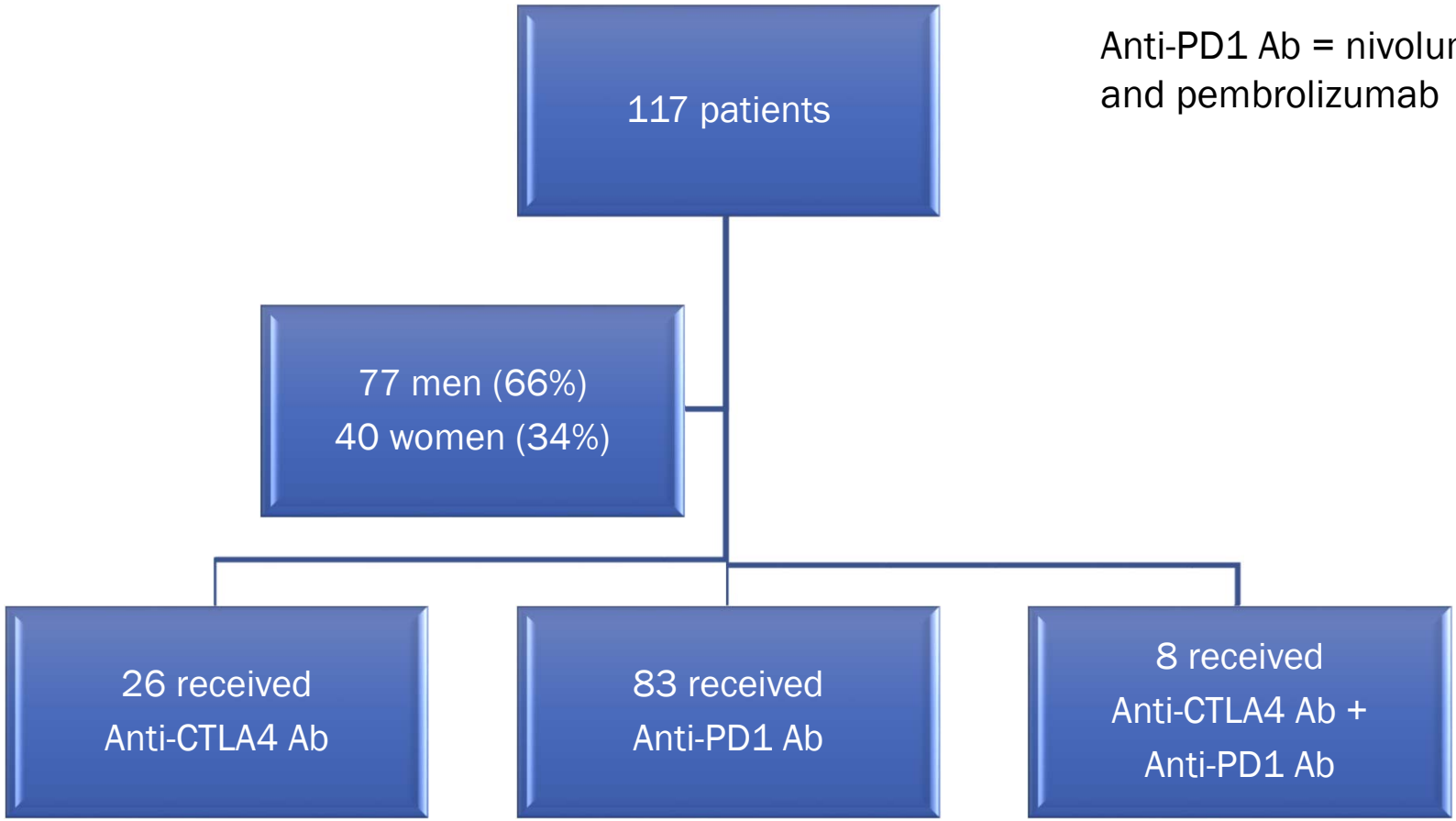
Methods

- A retrospective chart review was done of patients who received immune checkpoint inhibitors (ipilimumab, nivolumab, and pembrolizumab) at Scripps over 2 years (Jan 2015 – Dec 2016)
- Demographic data, number of infusions, and data involving the development and progression of endocrine disorders were collected
- Assessment of hypophysitis, thyroid dysfunction, adrenal insufficiency, and type 1 diabetes was done
- Endocrine disorder severity was graded from 1 – 4 based on the NIH Common Terminology Criteria for Adverse Events, with 1 being asymptomatic and 4 being life-threatening requiring urgent intervention

Results

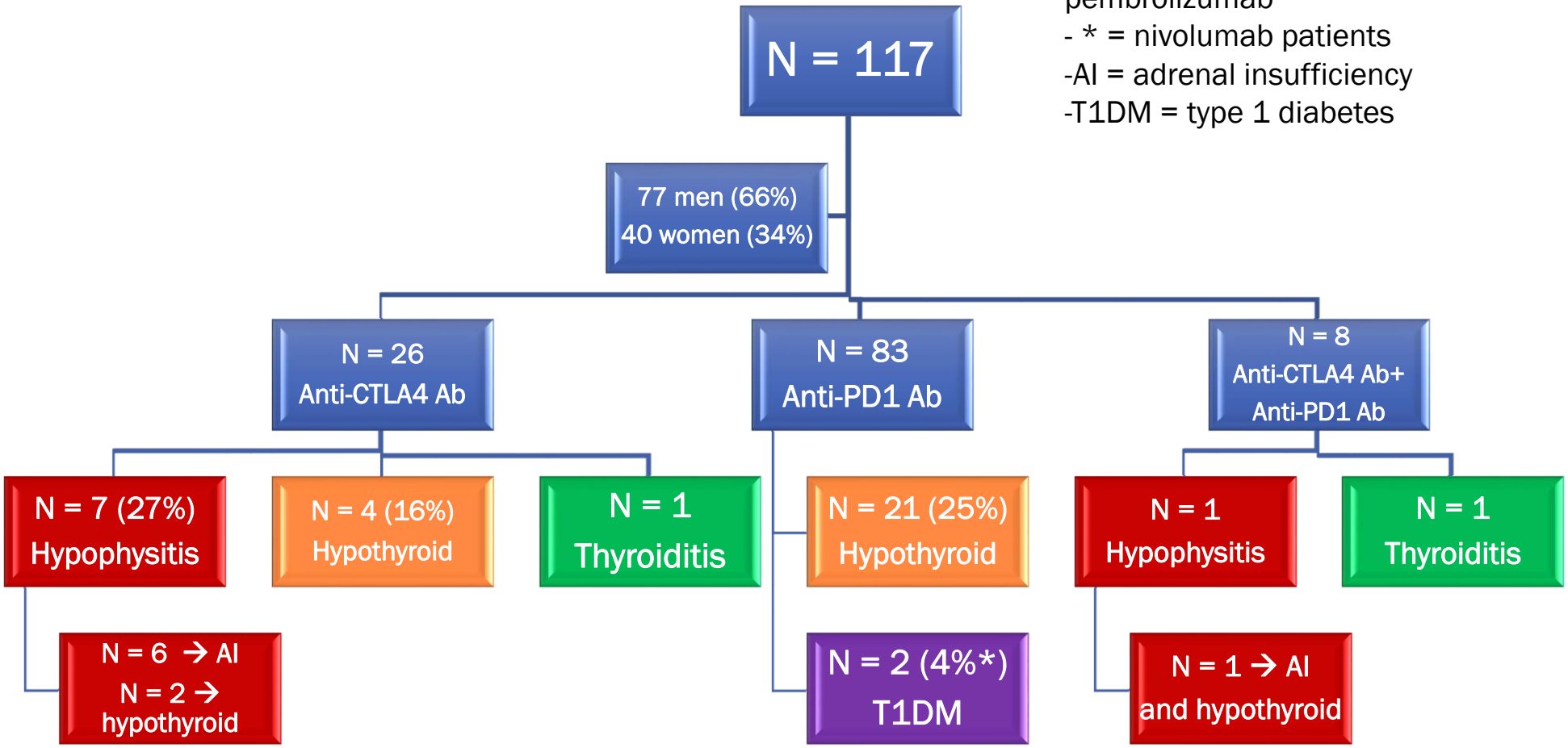
Anti-CTLA4 Ab = ipilimumab

Anti-PD1 Ab = nivolumab and pembrolizumab



Results

-Anti-CTLA4 Ab = ipilimumab
-Anti-PD1 Ab = nivolumab and pembrolizumab
- * = nivolumab patients
-AI = adrenal insufficiency
-T1DM = type 1 diabetes



Discussion

Our study found that the development of an endocrine disorder is very common with the use of immune checkpoint inhibitors

- 37 patients (32%) who received immune checkpoint inhibitor infusions developed some type of endocrine adverse event (irAE)
- Gender was not a risk factor for development of an endocrine irAE
  - *32% of women and 27% of men developed an endocrine irAE*

Discussion

- The most common endocrine irAEs were:
  - *Hypophysitis*
  - *Primary hypothyroidism*

- Early diagnosis and treatment of the endocrinopathy is important as it may prevent discontinuation of cancer treatment
  - *Patients who developed hypophysitis and T1DM had higher grade irAEs (grade 3), were hospitalized, and immunotherapy was eventually discontinued*

Discussion

- There is a lack of standardized screening protocols for the development of immune related endocrine adverse events
  - *Variability in obtaining baseline and subsequent thyroid function tests (TFTs)*
  - *Variability in pituitary hormone testing*

Discussion

It is important to monitor closely for development of irAEs throughout therapy given variable onset

- Most irAEs occurred between the 2nd and 5th infusion
- Six irAEs occurred after the 1st infusion
- One irAE occurred after 14 infusions
- Reviews (2016) indicate a median onset of 7 – 20 weeks, but current protocols recommend discontinuing screening at week 16[1,2]

Endocrine Disorder	Average number of doses given before development of irAE
Hypophysitis	3
Hypothyroidism	5.5
Thyroiditis	2
T1 diabetes	2

Discussion - Hypophysitis

- Hypophysitis was the most common irAE associated with anti-CTLA4 Ab therapy
  - *23% of those who received ipilimumab developed hypophysitis in our study*
  - *Incidence slightly higher than previously reported (0-17%)*[3]
  - *Lower incidence reported for anti-PD1 Ab therapy (0.9 -1.2%)*[1,4]

- ACTH and TSH are the most common hormone deficiencies reported
  - *Our study: 88% of those with hypophysitis had central adrenal insufficiency*
  - *Our study: 38% of those with hypophysitis had central hypothyroidism*

Discussion - Hypophysitis

Incidence was not associated with a higher dose of ipilimumab in our study

- Limitations: 2 doses unknown and small cohort

Ipilimumab Dose (mg/kg)	# of Patients Receiving Ipilimumab	# of Patients Who Developed Hypophysitis
3	22	5
10	10	1
Unknown	2	2
Total	34	8

Discussion - Hypophysitis

While other hormone axes may recover, development of central adrenal insufficiency is likely to be permanent[4]

- All 7 cases of central adrenal insufficiency did not have recovery of function in our study
  - *Mean follow up period: 9 months*

- 3 of 3 cases of central hypothyroidism have not resolved completely, although in 1 case, the dose requirement has decreased significantly
  - *Recovery has been reported in 37 – 50%*[5]

Discussion - Hypophysitis

High dose glucocorticoid therapy is currently recommended as standard treatment for hypophysitis and central adrenal insufficiency (AI)

- Albarel and colleagues did not show that high dose glucocorticoid therapy versus physiologic dosing improved the outcome[6]
- In our study, 7 of 7 patients with central AI received supraphysiologic glucocorticoid therapy and the axis did not recover
- Consider using physiologic glucocorticoid replacement dosing for treatment of AI to avoid adverse effects

Discussion – Primary Thyroid Disorders

- Thyroid disorders were the most common endocrine irAE with anti-PD1 Abs
  - *Our study: incidence of any thyroid disorder was 24% with anti-PD1 therapy*
  - *Reported incidence is 0 – 19% for anti-PD1 therapy, 0 – 7% for anti-CTLA4 therapy, and 18 – 24% for combination therapy*[1,4]

- Specifically, hypothyroidism was most commonly seen

Therapy	Hypothyroidism
Nivolumab	32%
Pembrolizumab	9%
Anti-PD1 Ab	23%

- Cases of thyrotoxicosis developed into thyroiditis or hypothyroidism

Discussion – Primary Thyroid Disorders

- Routine thyroid autoantibody testing was not done in our study, however, may predict those that will develop permanent dysfunction versus transient drug induced thyroiditis
  - *Weber and colleagues reported in a nivolumab series:*
    - 26% of patients who developed thyroid dysfunction had thyroid autoantibodies at baseline
    - 36% developed autoantibodies during immunotherapy[7]
  - *Consider TPO Ab testing if abnormal thyroid function tests develop*

- In our study, thyroid disease severity was grade 2 or less
  - *None of our patients had discontinuation of therapy due to thyroid disorder development*

Discussion - Type 1 Diabetes

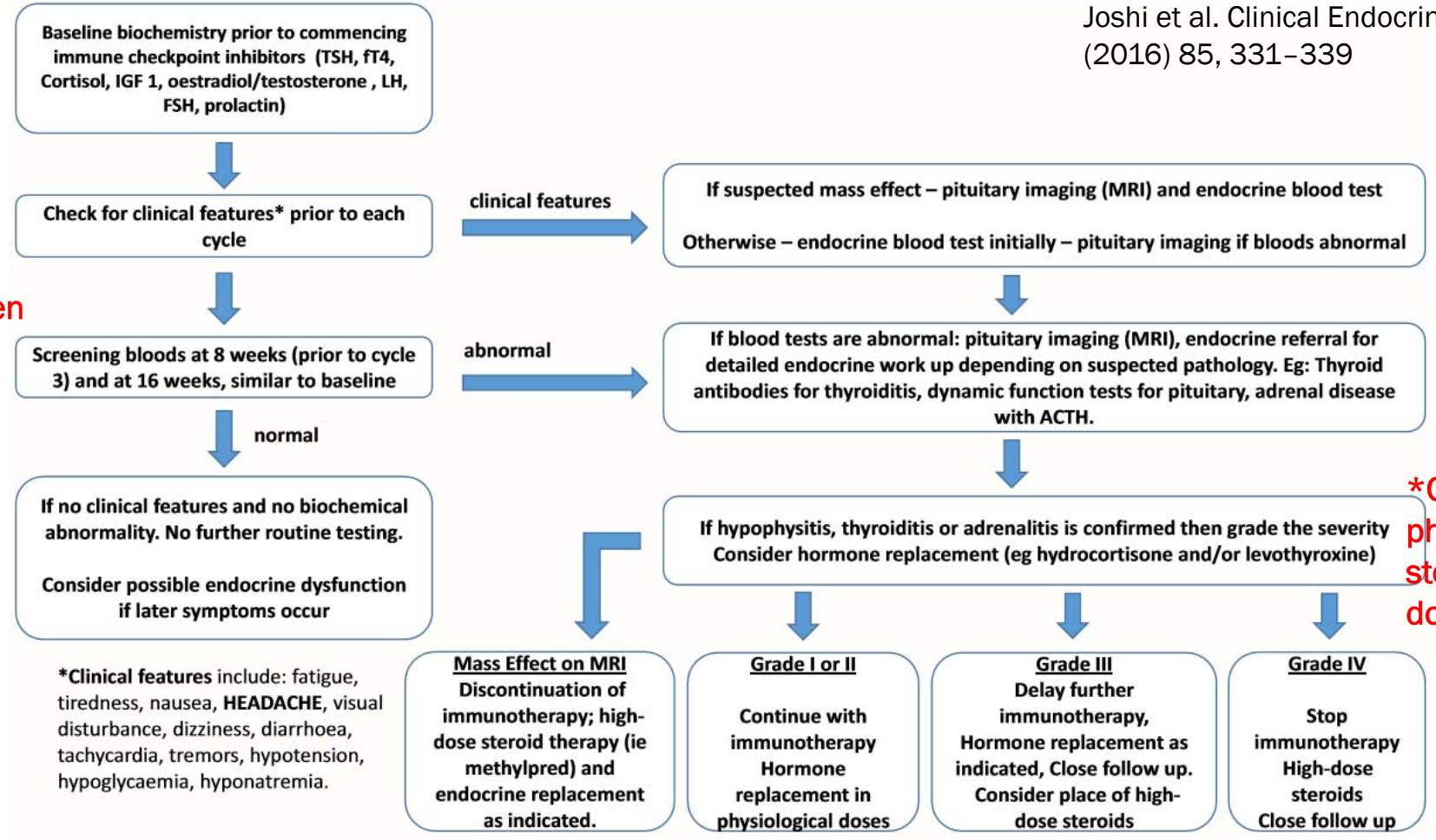
- New onset T1DM has been linked to checkpoint immunotherapy
- Rapid progression to insulin dependence in those with pre-existing diabetes has also been reported[8]
- The reported rate is 1% with each immune checkpoint inhibitor[9]
- In our study, there was a higher percentage (4%) of patients receiving nivolumab who developed T1DM
  - *New onset T1DM in one case*
  - *Rapid progression of diet controlled T2DM to insulin requiring in the second case*

Conclusion

- Endocrine immune related adverse events are common with the use of checkpoint immunotherapy
- While most endocrine irAE are mild, they can be life-threatening; rapid identification and treatment can prevent discontinuation of cancer treatment and improve outcomes
- Hypophysitis was the most common endocrine irAE associated with anti-CTLA4 Ab therapy
- Primary thyroid disorders (hypothyroidism) were the most common endocrine irAE associated with anti-PD1 Ab therapy

Conclusion - Suggested Algorithm

Joshi et al. Clinical Endocrinology (2016) 85, 331–339



*Consider BB before starting ATD given frequency of thyroiditis

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