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Thyroid Dysfunction in Patients Receiving Immune Checkpoint Inhibitors

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Background

- Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that target various immune checkpoints and are increasing in cancer treatment.
- ICIs reviewed in this study include the following: PD-1 inhibitors (nivolumab or pembrolizumab), PD-L1 inhibitors (durvalumab or atezolizumab), and CTLA-4 inhibitors (ipilimumab or tremelimumab).
- ICIs have been associated with endocrinopathies. However, literature describing the incidence of endocrinopathies associated with ICIs is limited in children.
- Common thyroid related adverse effects associated with ICI include hypothyroidism, hyperthyroidism, and thyrotoxicosis.
- Risk of primary thyroid dysfunction is higher in PD-1 and PD-L1 inhibitors.

Objectives

- We investigated the prevalence of thyroid dysfunction in patients who received ICIs at one pediatric institution.

Methods

Single center retrospective chart review from 2000 to November 2023

Inclusion Criteria:
- Received ≥1 of 6 ICIs

ICIs: nivolumab, pembrolizumab, durvalumab, atezolizumab, ipilimumab, or tremelimumab

Exclusion Criteria:
- Records unavailable to review (1 patient)
- Expired within 35 days of receiving initial ICI (6 patients)

20 patients included who received ≥1 ICI

Thyroid studies considered abnormal if outside reference range for age

Figure 1: Breakdown of patients included in study.

Medical Abbreviations:
TSH – thyroid stimulating hormone; FT4 – free thyroxine,
ICI – immune checkpoint inhibitor, TFT – thyroid function test

Results

Patient Characteristics and ICI Therapy Received

- Patient characteristics listed in table 2. At initial ICI received, patient ages ranged from 6.7-20.5 years (Figure 1). ICI therapy received shown in Table 2.

Patient Characteristics		
Sex	Male (n)	9
	Female (n)	11
Age at Diagnosis	Median (yr)	14.4
	Mean (yr)	12.5
Deceased	n	6
Relapse or Progression	N (%)	11 (55%)
Tumor Type	Blood (Leukemia/Lymphoma)	12 (60%)
	Solid	6 (30%)
	Melanoma	2 (10%)
Age at initial ICI	Median (yr)	14.9
	Mean (yr)	14.5

Table 1: Patient characteristics.

Immune Checkpoint Inhibitor Therapy	n (%)
Nivolumab	14 (70%)
Pembrolizumab	7 (35%)
Ipilimumab	1 (5%)
Atezolizumab	2 (10%)
Tremelimumab	2 (10%)
Durvalumab	2 (10%)
Received multiple ICIs	3 (15%)

Table 2: Immune checkpoint inhibitor therapy received.

Thyroid Dysfunction

- Thyroid function tests (TSH and/or FT4) were checked in 15 patients prior and 16 patients after initial ICI. 12 patients had thyroid function checked prior to and after ICI therapy
  - Prior to ICI therapy, 3 patients were diagnosed with hypothyroidism and treated with levothyroxine.
  - Following initial ICI therapy, 6 patients were treated with levothyroxine.
  - Thyroid dysfunction seen in patients who received PD-1 inhibitors. Highest incidence of thyroid dysfunction was seen with Nivolumab (Figure 2).

Thyroid Dysfunction	Number of Cases	Details
Hypothyroidism	5	•1 central hypothyroidism •3 new diagnoses •1 transient case
Hyperthyroidism	1	•Resolved with discontinuation of levothyroxine (previously diagnosed with acquired hypothyroidism)

Table 3: Description of thyroid dysfunction cases.

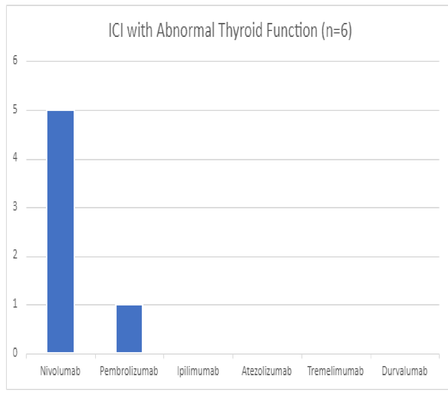

Figure 2: ICI therapy received in 6 patients with thyroid dysfunction.

Time to Thyroid Dysfunction		Avg (m)	Median (m)
New diagnosis (n=3)	Abnormal TFT	3.5	2.4
	Treatment	4.2	2.8
Previous diagnosis (n=2)	Abnormal TFT	0.85	n/a

Table 4: Time to thyroid dysfunction in those with abnormal thyroid labs following initial ICI separated by new diagnosis vs previous history of thyroid dysfunction.

Thyroid Dysfunction and Nivolumab

- Of those who received Nivolumab, 36% developed thyroid dysfunction (Figure 3).
- Of those who received Pembrolizumab, 14% developed thyroid dysfunction.

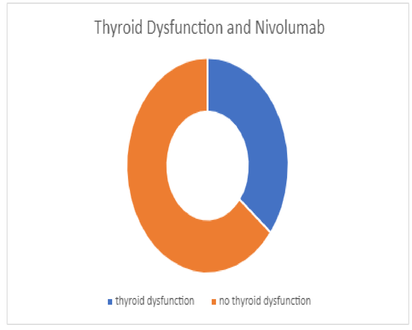

Figure 3: Immune checkpoint inhibitor therapy received in patients with thyroid dysfunction.

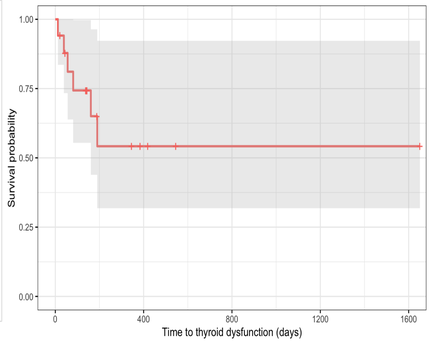

Figure 4: Kaplan-Meier estimate of median time to thyroid dysfunction.

Conclusions

- Thyroid dysfunction can be seen in pediatric patients receiving ICI therapy.
- This study supports monitoring TFTs including both TSH and FT4 as can see both central and primary hypothyroidism
- Time to thyroid dysfunction is within several months of receiving initial dose of ICI. However, in patients with previous history of thyroid dysfunction, thyroid dysfunction may occur earlier and may require a dose adjustment in current thyroid medication
- Highest risk of thyroid dysfunction appears to be in those who received Nivolumab
- Study limited by small sample size and no comparison group.
- Future directions include investigating additional endocrinopathies in children such as diabetes mellitus or adrenal insufficiency and increasing sample size.

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