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Ipilimumab-induced hypophysitis, a single academic center experience

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Abstract

Background Immune checkpoint inhibitors, single or in combination, have recently become a cornerstone for the treatment of many malignancies. Ipilimumab, a CTLA-4 inhibitor, was initially FDA approved for treatment of unresectable or metastatic melanoma and subsequently in combination therapy for other cancers. Ipilimumab-induced hypophysitis (IH) risk of development varies in different studies between 0 and 17%. Furthermore, little is known on how to predict which patients will develop IH and its impact on efficacy of Ipilimumab and survival for these patients. Here we reviewed IH and its impact on progression-free survival (PFS) and overall survival (OS).

Methods Retrospective, IRB- approved review of consecutive 117 melanoma patients who received ipilimumab between 2011 and 2016 was undertaken. Demographic and clinical characteristics, treatment timing and doses, time to progression after therapy, and survival data were reviewed. Patients were predefined in two groups: patients with and without IH. Descriptive statistics were used to summarize the demographic and clinical characteristics of the study sample. All values are shown as means and standard deviation [mean (SD)] unless indicated otherwise. $P < 0.05$ was considered to be statistically significant.

Results Of the 117 patients, 15 (12.8%) with a median age of 62.1 years developed IH. In the IH cohort, 10 (66.7%) were male and were significantly older than females (median 67.7 vs. 50.8; $P = 0.009$). This difference was not seen in non-IH group. Male patients with IH were significantly older than males without IH (67.7 vs. 56.4 years, $P = 0.020$), however this difference was not observed in females. No patient who received prior cancer systemic therapy (0/30) developed IH vs. 17.2% (15/72) without prior therapy developed IH (OR 0.00; 95% CI 0.00 to 0.73, $P = 0.011$). Between IH and non-IH patients, there was no difference in gender, race, ethnicity, BMI, diabetes or autoimmune disease at baseline, number of administered ipilimumab cycles, presence of primary melanoma lesion, or BRAF status. IH and non-IH patients had a similar median PFS (8.1 vs. 6.8 months, HR = 0.51, 95% CI 0.24 to 1.05 $P = 0.062$) and OS (53.3 vs. 29.5 months; HR 0.66, 95% CI 0.30 to 1.46; $P = 0.307$).

Conclusion In this study of melanoma patients treated with Ipilimumab, risk of developing IH was high (almost 13%). Older age in men and no prior cancer therapy were associated with IH higher risk. Development of IH was not associated with PFS or OS. Increased use of immune checkpoint inhibitors in the future will impact IH overall risk, thus awareness is needed. Given the lack of reliable identifiable risk factors, close monitoring of signs and symptoms after each therapy cycle is critical for early detection and treatment of hypophysitis.

Keywords Malignant melanoma · Ipilimumab · Hypophysitis · Immunotherapy · Immune related adverse side effects

Introduction

Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is an inhibitory molecule on T-cells which promotes downregulation of T cell activation and it's blockage potentiates antitumor T cell immune response [1]. Ipilimumab is a fully human cytotoxic CTLA-4 antibody approved as a single agent for

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treatment of unresectable or metastatic melanoma and as adjuvant therapy for cutaneous melanoma with pathologic involvement of regional lymph nodes after complete resection [2]. In combination with nivolumab, it is approved for treatment of metastatic melanoma, intermediate or poor risk renal cell carcinoma and mismatch-repair deficient or microsatellite instability-high metastatic colorectal cancer [2].

Stronger expression of CTLA-4 has been found in patients with more severe IH. It has been proposed that blocking of pituitary CTLA-4 by anti-CTLA agents triggers activation of type 2 (complement) and type 4 (autoreactive T cells) hypersensitivity reactions [3]. Expression of PD-1 or PD-L1 by the pituitary has not yet been demonstrated, consistent with the clinical observation that PD-1 or PD-L1 inhibitors are less frequently associated with IH compared with CTLA-4 inhibitors [4].

Immune checkpoint inhibitors like ipilimumab are effective in cancer treatment, but increased T-cell activation by these therapies can result in immune-related adverse effects (irAEs). These irAEs result from damage to any affected organ system and range from pneumonitis, rash, colitis to endocrinopathies [2, 5, 6]. The most common endocrinopathy and one of the most concerning toxicity with ipilimumab is hypophysitis [5, 6]. Ipilimumab-induced hypophysitis (IH) is caused by type II hypersensitivity reaction as a result of CTLA-4 antibody binding to antigens on pituitary cells leading to complement activation and destruction of pituitary gland [5]. In general, patients with IH present with nonspecific symptoms most commonly headache, weakness, and fatigue [5]. In suspected hypophysitis, NCCN guidelines recommends laboratory evaluation of AM cortisol, follicle stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), free thyroxine (Free T4), testosterone in men, and estrogen in premenopausal women. If the patient is symptomatic, imaging the pituitary via MRI with pituitary and sellar cuts is advised for structural assessment [7]. Management strategies depend on the severity of IH and may include withholding or discontinuing ipilimumab, endocrine consultation, hormone replacement as indicated, and in severe cases high dose glucocorticoid (GC) administration [7, 8]. For patients who have persistent hormonal deficiencies from IH, it is imperative to educate patients on the need for steroid dosing for future stress episodes such as infections, trauma, or surgeries. Use of alert bracelets for such situations is strongly recommended [7].

Currently, controversy exists with regards to survival and treatment among patients with IH with some studies reporting no outcome improvement [9] and increased mortality with use of high dose GC [10] while others reporting improved survival and anti-tumor response with development of IH [11]. Till now we do not have well-defined predictors to ascertain which patients will develop IH. With the advent of multiple treatment therapies for advanced melanoma, these tools can help select patients for appropriate treatments based on both efficacy and with least toxicities. To achieve this objective, we conducted a retrospective review of patients with metastatic melanoma treated with ipilimumab to delineate potential predicators of IH within our cohort at the University of Iowa.

Methods

A total of consecutive 117 patients were reviewed in this study. Study of all patients with metastatic melanoma treated at University of Iowa Holden Comprehensive Cancer Center from November 2008 until September 2015 was approved by the institutional review board. Patients received ipilimumab for advanced melanoma either after FDA approval (3 mg/kg) or as part of other research protocols ongoing at our institution (3 mg/kg or 10 mg/kg; NCT201107795, NCT201211780, NCT201311715, NCT201304510, NCT201408502). We reviewed in detail patient medical records including patient encounters, laboratory data, radiological images, and medication records. All patients except one female patient (Table 1, case number 1) received all their care at University of Iowa after diagnosis of IH. Median follow up for patients diagnosed with IH was 52.7 months (95% CI 32.6 to 64.1 months). Serum hormone measurements including: TSH, Free T4, cortisol, ACTH, LH, FSH, total testosterone, estradiol, and IGF-1 were measured to varying frequencies as per treating physician discretion. Patients were evaluated for IH after development of suggestive symptoms such as fatigue or headache. Clinical diagnosis of IH was supported by radiographic findings and/or laboratory evaluation. MRI findings supportive of the IH diagnosis included homogenous enhancement of the pituitary, diffuse symmetric gland enlargement, midline stalk thickening, absence of a posterior bright spot, an intact sellar floor, and normal sellar size based on prior literature [12, 13] = Laboratory evaluation supportive of IH included: adrenal insufficiency (normal or suppressed ACTH with low cortisol), hypothyroidism (normal or suppressed TSH with low free T4), or gonadal dysfunction (low total testosterone or estradiol with inappropriately low or normal LH or FSH).

Values are summarized as mean and standard deviation [mean (sd)] unless otherwise indicated. Two sample independent *t*-tests were used to compare continuous measures between groups; non-parametric methods used where appropriate. Categorical outcomes were assessed using Fisher's exact test and reported as odd ratios and confidence intervals. Overall survival (OS) is determined from treatment start until death from any cause. Progression-free survival (PFS) from treatment start until disease progression or death. Time to progression (TTP) from treatment start until disease progression (not including deaths). Kaplan–Meier method

Table 1 Characteristics of patients diagnosed with ipilimumab-induced hypophysitis

Case number	Age	Gender	Ipi dosage mg/kg	Number of cycles at diagnosis	Overall survival after Ipi (months)	Time to progression (months)	Other irAE(s)
1	65	Female	3	2	39.5+	39.5	Rash
2	47	Female	3	3	64.2+	64.2	Rash, myalgias
3	63	Male	3	3	84.8+	32.3	None
4	64	Male	3	4	17.5	4.6	None
5	64	Male	10	2	53.3	7.5	Colitis
6	55	Male	3	4	44.9	6.4	None
7	78	Male	3	4	14.9	5.5	None
8	88	Male	3	3	52.6+	2.8	Rash
9	78	Male	3	3	17.2	3.7	Colitis
10	47	Female	3	3	40.4+	40.4	None
11	60	Male	3	2	26.7	8.1	None
12	39	Female	10	2	32.6+	32.6	Colitis
13	56	Female	3	4	10.2	2.5	None
14	64	Male	3	3	54.4+	54.4	Colitis
15	63	Male	3	3	42.9+	42.9	Rash

+ Indicates that the patient was alive at time of last follow-up

was used to graphically illustrate the estimated survival curves, and log rank test was used to compare unadjusted OS, TTP, and PFS between groups. We also estimated the hazard ratio for patient group using cox proportional hazard regression model. Statistical analysis was performed using R: A Language and Environment for Statistical Computing. $P < 0.05$ was considered to be statistically significant.

Results

A total of 15 out of 117 patients (Tables 1 and 2) in our cohort were diagnosed with IH during course of treatment of ipilimumab (12.8%). The majority (13/15) of patients with IH were treated with a dose of 3 mg/kg (86.7%) of ipilimumab with 2 receiving 10 mg/kg (13.3%). Of the patients, 10 were male and 5 were female out of 74 male and 43 female patients, respectively. The proportion of males with IH was 13.5% compared to 11.6% for females (P = 1.0). For patients who received prior chemotherapy, no patient developed IH (0/30) while 17.2% (15/87) patients who were treatment naïve developed IH. The average age of patients who were diagnosed with IH was 62.1 years (95% CI 55.0 to 69.1) compared to 57.5 (95% CI 54.4 to 60.5; P = 0.271). Among patients with IH, males were significantly older than females [67.7 years (95% CI 60.4 to 75.0 years) vs. 50.8 (95% CI 38.4 to 63.2), P = 0.009]. For patients without IH, there was no significant difference in age for males compared to females [56.4 years (95% CI 52.7 to 60.0) vs. 59.2 years (95% CI 53.7 to 64.7), P = 0.367). Males were also significantly older who developed IH compared to males who did not [67.7 years (95% CI 60.4 to 75.0) vs. 56.4 years (95% CI 52.7 to 60.0), P = 0.020]. There was no significant difference in number of ipilimumab treatment cycles and development of IH [3.0 cycles (95% CI 2.6 to 3.4) vs. 3.5 cycles (95% CI 3.3 to 3.7), P = 0.087]. Between the two groups there were no significant differences in patients for race, diabetes, BMI, presence of baseline autoimmune condition, presence of primary melanoma lesion, or BRAF results (see Table 3).

For patients with hypophysitis (Tables 1 and 2), all were symptomatic at diagnosis. IH related symptoms reported were headaches (13 patients) followed by fatigue (9 patients), hyponatremia (5 patients), blurry vision, weakness (both 4 patients), and decreased libido (2 patients). Notably for the four patients with visual disturbance, they had resolution of symptoms after initiation of GC therapy for IH. Out of the 15 IH patients, 8 patients reported other immune related adverse effects (irAE). Colitis and rash were both reported in 4 patients. One patient reported myalgias. For patients without IH, irAEs were documented in 52.0% (53/102). Overall, there were no significant differences in development of irAEs for patients with IH and those without (P = 0.702).

Multiple anterior pituitary hormonal deficiencies were noted in our patient cohort (Table 2). Adrenal deficiency was diagnosed clinically in all 15 patients. Diagnosis was supported with morning serum cortisol under 3 µg/dl (9 patients) at the time of presentation. Of these patients, plasma ACTH was measured under 10 pg/ml in 4 patients. For the remaining 6 patients with clinical suspicion for adrenal deficiency, they either received corticosteroids prior to the measurement of adrenal axis labs (4 patients) or had

Table 2 Characteristics of patients diagnosed with ipilimumab-induced hypophysitis continued

Case number	Presenting signs and symptoms	Hormonal deficiencies	Treatment (course)[a]	Hormonal access recovery	MRI timing (days)[b]	MRI findings (mm)
1	HA, BV	Ad, Td (HypoTh)	GC HD (6 weeks) then HC RD, T	None	5	PB 14.1×11.3 PS 3.4
2	HA, F, W, hypoNa	Cd, Td	GC HD (NA) then HC RD, T	None	NA	NA
3	HA, BV, F, DL	Ad, Td, Gd	GC HD (4 weeks) then HC RD, T, TR	None	14	PB 10.4×10.3 PS 3.2
4	F, W	Ad[c], Td, Gd	GC HD (2 weeks) then HC RD, T	Ad, Td none Gd 8 weeks	16	PB 11.5×5.3 PS 2.2
5	HA	Ad, Td (HypoTh), Gd	GC HD (6 weeks) then HC RD, T (chronic dose)	Ad none Td 4 weeks Gd 8 weeks	8	PB 12.2×8.9 PS 3.9
6	HA	Ad[c]	GC HD (4 weeks) then HC RD	None	7	PB 11.5×10.2 PS 4.2
7	F, W, hypoNa	Ad[c]	GC HD (6 weeks) then HC RD	None	1	PB 12.6×7.6 PS 3.2
8	HA, F, W	Ad[c], Td, Gd	GC HD (3 weeks) then HC RD, T, TR	Ad, Gd none Td partial 8 weeks	4	PB 10.1×8 PS 2.9
9	HA, hypoNa	Ad, Td, Gd	GC HD (4 weeks) then HC RD	Cd, Gd none Td 2 weeks	34	PB 8.2×5.2 PS 2.1
10	HA, F, BV	Ad, Td	GC HD (4 weeks) then HC RD (7 weeks), T	Ad 11 weeks Td 15 weeks	5	PB 15.0×9.8 PS 3.8
11	HA, F, hypoNa	Ad, Td, Gd	GC HD (4 weeks) then HC RD, T	Ad none Td none Gd 8 weeks	10	PB 12.3×11.1 PS 2.2
12	HA, F	Ad[c], Td	GC HD (8 weeks) then HC RD, T	None	14	PB 14.2×10.5 PS 3.9
13	HA, BV, F, hypoNa	Ad[c], Td	GC LD (3 weeks) then HC RD, T	None	6	PB 12.8×12.1 PS 4.2
14	HA	Ad, Gd	GC HD (8 weeks) then HC RD, T (chronic dose)	Ad none Gd 8 weeks	8	PB 12×10.4 PS 4.8
15	HA, DL	Cd, Td, Gd	GC HD (4 weeks) then HC RD, T, TR	None	4	PB 10.7×10.2 PS na

HA headache, *BV* blurry vision, *F* fatigue, *W* weakness, *DL* decreased libido, *hypoNa* hyponatremia *Ad* adrenal deficiency, *Td* thyrotrope deficiency, *HypoTh* pretreatment hypothyroid, *Gd* gonadotroph deficiency, *GC* glucocorticoids, *HD* high dose, *LD* low dose, *RD* replacement dose, *T* l-thyroxine, *TR* testosterone replacement, *PB* pituitary body, *PS* pituitary stalk

[a]Hydrocortisone and L-thyroxine treatment courses indefinite unless otherwise noted

[b]Days from symptom onset

[c]Adrenal deficiency diagnosed clinically as steroids administered prior to cortisol or ACTH measurement or secondary adrenal insufficiency noted on subsequent testing

evidence of secondary adrenal insufficiency on subsequent testing during steroid tapering (2 patients). Central hypothyroidism was diagnosed in 12 out of 15 patients. Diagnosis was supported by in all 12 patients with low or inappropriately normal TSH. Eleven patients had FT4 levels below the normal value. Of the 3 remaining patients, one had hypothyroidism at baseline and was hyperthyroid at time of diagnosis from excessive L-thyroxine replacement, and the other 2 patients did not have thyroid labs measured. Gonadal deficiency was diagnosed in 8 out of 15 patients, all of whom were men. Diagnosis supported by at least two measurements of low total testosterone levels. Total testosterone levels were undetectable in 4 patients and below 100 ng/dl in the remaining 4 patients. FSH and LH levels were measured in 4 of these 8 patients and were inappropriately low. Of the remaining 7 patients, gonadal hormone labs were not checked, and 1 woman tested was not deficient. There were no cases of diabetes insipidus.

Of the 15 patients, 7 patients had some degree of hormonal axis recovery. Gonadal functional recovery was

Table 3 Characteristics of patients with and without hypophysitis

	+ Hypophysitis	No hypophysitis	P value
Number	15	102	
Age, mean (SD)	62.07 (12.76)	57.46 (15.34)	0.271
Gender (%)			
Female	5 (33.3)	38 (37.3)	1.0
Male	10 (66.7)	64 (62.7)	
Race (%)			
Caucasian	15 (100.0)	99 (99.0)	1.0
Hispanic	0 (0.0)	1 (1.0)	
Ethnicity (%)			
Non-Hispanic	15 (100)	100 (99.0)	1.0
Hispanic	0 (0.0	1 (1)	
Diabetes (%)			
Yes	2 (13.3)	13 (13.7)	1.0
No	13 (86.7)	82 (86.3)	
BMI, mean (SD)	29.72 (4.36)	29.39 (6.94)	0.859
Baseline autoimmune disease (%)			
Yes	2 (13.3)	1 (1.0)	0.045
No	13 (86.7)	98 (99.0)	
Number of Ipi cycles, mean (SD)	3.00 (0.76)	3.49 (1.05)	0.087
Weeks to IH diagnosis, median (IQR)	10.25 (9.11, 18.93)	NA [NA, NA]	NA
Survival time after Ipi in months, median (95% CI)	53.3 (17.3 to NA)	29.5 (18.8 to NA)	0.307
Prior chemotherapy (%)			
Yes	0 (0.0)	30 (29.4)	0.011
No	15 (100.0)	72 (70.6)	
BRAF mutation (%)			
Positive	4 (36.4)	35 (44.3)	0.751
Negative	7 (63.6)	44 (55.7)	
Melanoma with known primary lesion			
Yes	14 (93.3)	85 (85.9)	0.688
No	1 (6.7)	14 (14.1)	

SD standard deviation, *IQR* interquartile range, *95% CI* 95% confidence interval, *IH* ipilimumab-induced hypophysitis, *Ipi* ipilimumab

appreciated in 4 patients. There was full thyroid functional recovery in 3 patients and partial recovery in 1 patient. Only 1 patient had adrenal axis recovery.

Of the 15 patients who developed IH, all 15 patients are documented to have received corticosteroids for treatment. High dose corticosteroids were used in 12 of the patients ($\geq$ 40 mg prednisone daily) at initial treatment followed by a steroid taper. Low dose steroids were used in 3 patients ($<$ 80 mg prednisone daily). The average steroid course was 4.7 weeks including taper. All patients were transitioned to hydrocortisone replacement. Only 1 patient was subsequently able to be weaned off hydrocortisone with adrenal axis recovery. Twelve patients received L-thyroxine replacement and 3 patients received testosterone replacement.

MRI demonstrating mild to moderate diffuse pituitary enlargement supporting IH diagnosis was present in 12 out of 15 of the cases (80%, Table 2). Two of the remaining patients diagnosed with IH did not have MR imaging done at time of IH presentation (within 30 days). The other patient did not have pituitary enhancement or enlargement appreciated. No optic chiasm compression was appreciated in any patient including the 4 patients who developed visual disturbance.

Lab values measured prior to ipilimumab and post administration included: albumin, total protein, Alanine transaminases (ALT), aspartate transaminases (AST), alkaline phosphatase (ALP), and total bilirubin. There was a significant difference for albumin lab value post ipilimumab for patients with IH and no IH [4.20 vs. 4.00 (P = 0.017)]. There was no difference for albumin on patients with and without IH prior to ipilimumab [4.30 vs. 4.20 (P = 0.265)]. There was not a significant difference noted between patients with IH and those without for all other lab values drawn for prior and post ipilimumab administration.

There was no statistically significant difference detected in overall survival between patients that were diagnosed with IH and those that did not [HR 0.66] (95% CI 0.30 to 1.46 P = 0.307) (See Fig. 1). The median overall survival in patients with IH is estimated to be about 53.3 months (95% CI 17.3 to NA). Median overall survival for patients without IH is estimated to be about 29.5 months (95% CI 18.8 to NA). For time to progression (see Fig. 2), there was no statistically significant difference between patients diagnosed with IH and those who were not (P = 0.166). For the fifteen patients identified to have IH, eight had progression of disease with median time to progression estimated to be 8.1 months (95% CI 3.7 to NA months). For the ninety-seven patients without IH, seventy-two had progression with

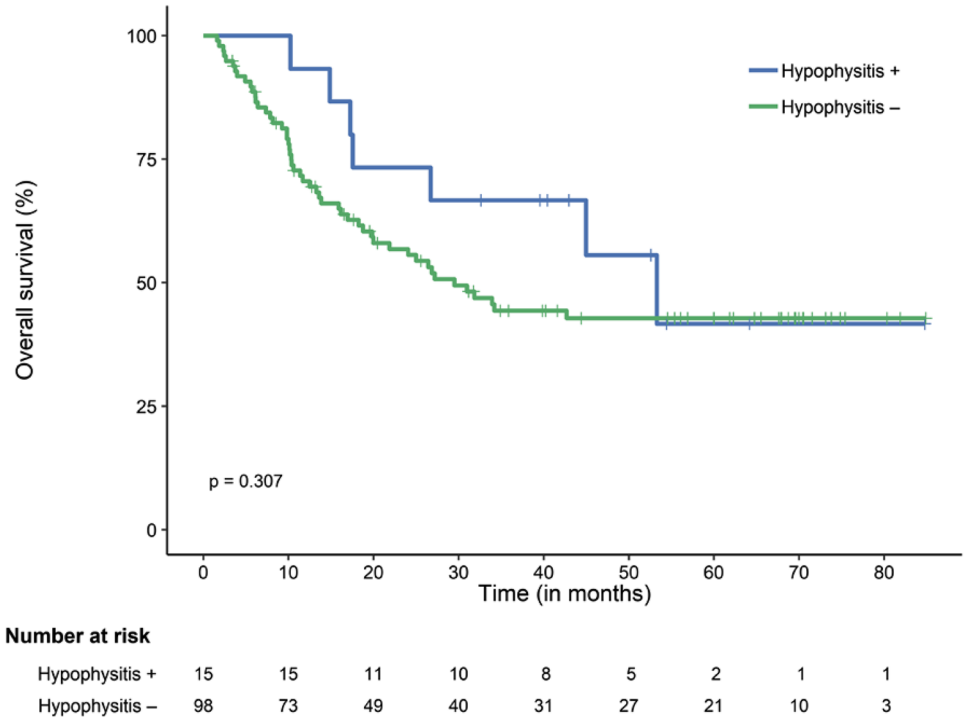

Fig. 1 Overall survival for patients with and without hypophysitis

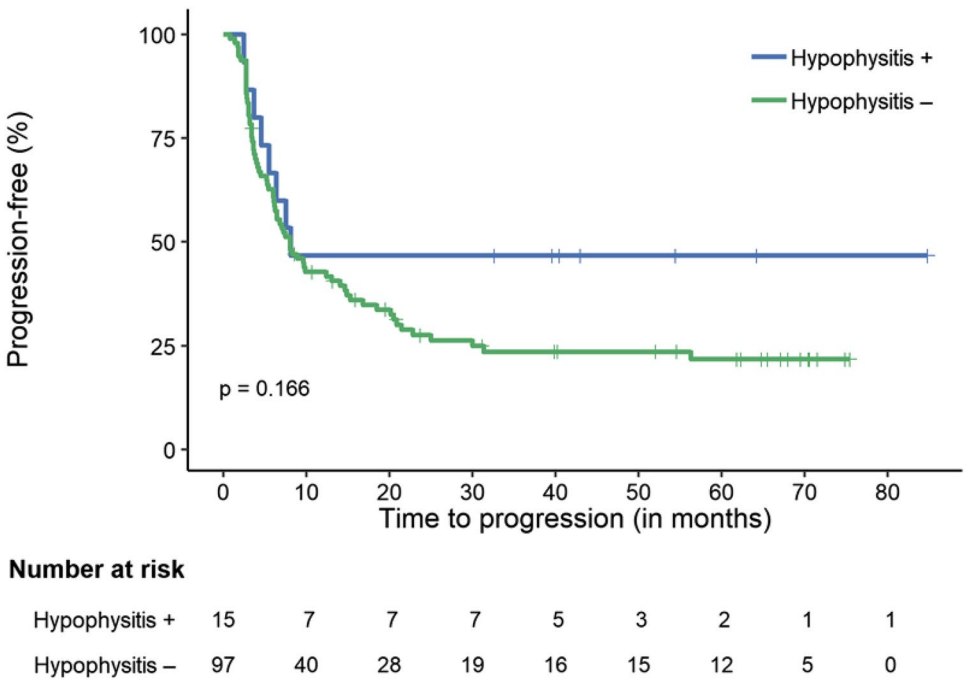

Fig. 2 Time to progression for patients with and without hypophysitis

median time to progression estimated at 8 months (95% CI 6.1 to 14 months). For progression-free survival (See Fig. 3), there was no statistically significant difference between IH group and non-IH group (P = 0.062). For the sample data of 115 patients, eighty-seven had progressed or died (75.7%) with estimated median PFS to be 7 months (95% CI 5.4 to 9.7 months). For the fifteen patients with IH, eight had progression or died (53.3%) with estimated PFS of 8.1 months (95% CI 3.7 months to NA months). For the ninety-seven without IH, seventy-eight had progressed or died with PFS estimated to be 6.8 months (95% CI 5.2 to 9.7 months).

Discussion

In our large cohort of patients with metastatic melanoma, risk of developing IH was high, approaching 13%. IH incidence in the literature varies significantly, ranging from 0 to 17% with most studies describing ~ 10–15% [5, 14, 15]. A meta-analysis of 34 studies by Barroso-Sousa et al. reported an incidence of 3.2% in patients receiving CTLA-4 inhibitors [15]. This may have been limited by underreporting in earlier trials as clinical recognition is an important factor in the workup for IH and diagnosis. Older trials did not have standardized assessment tools for endocrine irAEs including measurement of serum hormones in all patients or had limited data on just TSH and ACTH rather than complete panels. Due to non-specific symptoms of IH and resolution of pituitary inflammation without treatment, many patients would go unrecognized without appropriate clinical suspicion. Patients usually do not recover anterior pituitary function after development of IH [6, 11]. Although our study did not appreciate a statistically significant difference in IH development by gender, male gender has been associated with increased incidence of IH even after adjustment of differing melanoma incidence [8, 16]. However, in our cohort male patients were significantly older at diagnosis. Older age is associated with increased incidence of advanced melanoma and is attributed as a risk factor for development of IH [11, 16] which we appreciated in our cohort of patients.

There was no statistically significant overall survival between patients who developed IH and those who did not, there was trend towards improved survival for IH patients. However, due to limited power from a low number of IH patients, further studies with a larger number of patients may show statistically significant difference in overall survival. A statistically significant survival advantage was seen by Faje et al. (19.4 vs. 9.8 months) which was replicated in a larger cohort of patients [11, 14] Multiple studies have showed a positive correlation between development of irAE and cancer response, however they are largely retrospective and have limited patient samples [17].

It appears that many irAEs attributed to ipilimumab appear to be dose-related including rash, fatigue, and diarrhea [1, 18]. There is conflicting data whether the risk of IH development is dose-related as some studies have not shown differences in IH rates between administered doses [11, 14], while a recent phase 3 trial showing an association between higher rate of IH with the treatment dose [19]. As most patients in our IH cohort received a dose of 3 mg/kg

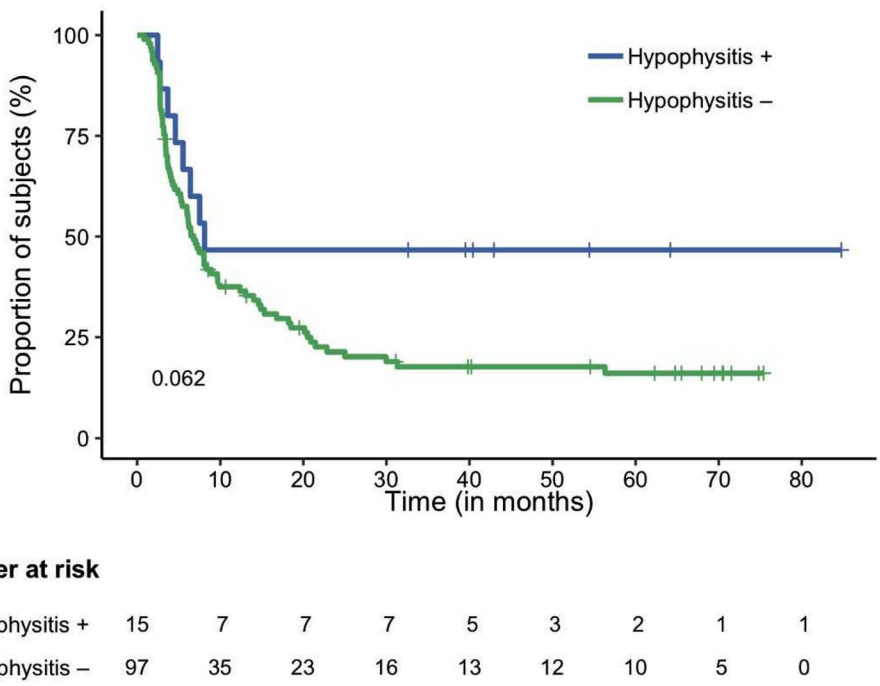

Fig. 3 Progression-free survival for patients with and without hypophysitis

of ipilimumab (13/15) with only 2 patients receiving high dose of 10 mg/kg we could not evaluate any differences in risk of IH development between patients receiving low and high doses.

One other interesting finding in our study was that patients who were treatment naïve were at an increased risk of developing IH. Potentially this is due to immune cell depletion from cytotoxic chemotherapy and brain radiotherapy as suggested in earlier studies [8, 20]. However, it has been postulated that combination therapy with immunotherapy with either radiotherapy or chemotherapy may improve survival which is counter to the improved survival seen with IH development. This improved survival is theorized to be secondary to improved tumor antigen presentation from cytotoxic chemotherapy or radiotherapy. Multiple trials are investigating this potential benefit in combination with checkpoint inhibitors [21].

Management of IH is still controversial. At the time of IH diagnosis in our cohort, the standard of care was high dose GC (methylprednisolone 1–2 mg/kg IV or prednisone 0.5–1 mg/kg) [8, 22]. Fourteen of the 15 patients with IH received equivalent to one of these regimens. Recent studies have not shown a benefit in recovery of pituitary function or mortality with high dose GC [16], and furthermore they have been associated with increased mortality [10]. Current guidelines recommend high-dose GC only in symptomatic patients like with headaches, nausea, vomiting, and fevers. Holding immunotherapy in selected cases [23], endocrine consultation and other pituitary hormone replacement as indicated are also recommended [7]. Patients presenting with adrenal crisis or severe hyponatremia should be treated with stress dose GC (intravenous hydrocortisone is preferred) and fluids as per current Endocrine Society guidelines [17].

In most studies, pituitary enlargement resolved quickly (within 3 months) but adrenal deficiency persisted long-term in majority of patients irrespective of GC dose [4, 6]. Recovery of other pituitary functions is more variable, but thyroid and gonadal axes have a more favorable prognosis [11, 16].

With the increased use of anti-CTLA-4 monoclonal antibodies especially in combination with anti-PD-1 antibodies, clinical suspicion is of vital importance in diagnosing IH early in patients to appropriately manage to improve outcomes. Anti-PD-1 and anti PD-L1 antibodies induce less hypophysitis [24], but in some cases, because they can induce thyroiditis or primary adrenal insufficiency, clinical picture and diagnosis can be more complex in patients on combination Ipilimumab- anti-PD1/PD-L1. Predictive factors as in our study, including male gender, advanced age, and treatment naivety can assist guidance of treatment choice in new patient evaluations. However, further studies of outcomes and factors on larger patient populations are warranted to elucidate other factors which may assist in decision making.

Strength of the study include uniform evaluation of all patients in a single center and long-term follow-up. Limitations include retrospective design, low number of IH patients, and absence of imaging in some cases. Some patients also had limited endocrinological laboratory data available at time of IH diagnosis complicating the evaluation of hormonal axis deficiencies. Furthermore, based on treatment protocols at that time, patients were treated with low dose Ipilimumab and high dose GC, making comparisons impossible between different treatment groups.

Management of IH has been controversial and more studies examining patients who had various GC treatment strategies are needed to understand how to best improve patient's outcomes. Until additional evidence is derived, clinicians need to be aware of this frequent adverse reaction in anti-CTLA therapy and ensure prompt appropriate treatment.

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Compliance with ethical standards

Conflict of interest Travis Snyders declares that he has no conflict of interest. Daniel Chakos declares that he has no conflict of interest. Umang Swami declares that he has no conflict of interest. Emile Latour declares that he has no conflict of interest. Yiyi Chen declares that she has no conflicts of interest. Maria Fleseriu declares that she has no conflict of interest. Mohammed Milhem is a member of advisory boards for Amgen, Trieza, Biontech, Blueprint medicines corporation, Immunocore, and Array BioPharma, Inc. Yousef Zakharia is a member of advisory boards for Amgen, Roche diagnostics, Novartis, Jansen, Eisai, Exelixis, Castle Bioscience, Array, and Bayer. Roula Zahr declares that she has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent The Institutional Review Board at the University of Iowa Hospitals and Clinics approved this study. As this was a retrospective review of patient data, individual informed consent was exempted by the Institutional review board.

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