Risk Factors Associated With Upper Gastrointestinal Bleeding In Cancer Patients Exposed To Immune Checkpoint Inhibitors

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Background

- Immune checkpoint inhibitors (ICIs) have emerged as effective treatment options for many advanced malignancies
- Gastrointestinal (GI) side effects are amongst the most commonly reported immune related adverse events (irAEs)
- Currently, limited data exists on upper GI bleed (UGIB) in patients exposed to ICIs
- The aim of this study was to evaluate the characteristics and risk factors associated with UGIB among cancer patients treated with ICIs.

Methods

- We performed a retrospective study on all cancer patients from Cleveland Clinic health system who received treatment with ICI's until June 2021
- Only the patients with clinical and endoscopic evidence of upper GI bleed were included in the study.
- The study group (GI Bleed) was matched with control group (non-Bleeders) in 1:3.

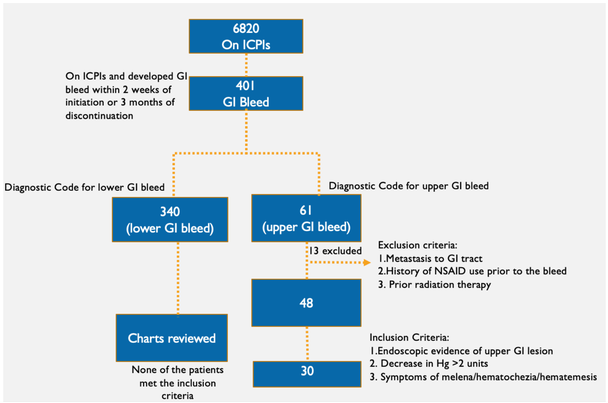

Table1: Clinical characteristics of bleeding group

Duration of steroid use to onset of GI bleeding, month (SD)	28.1 (32.7)
Duration of ICI use to UGIB onset, month, mean (SD)	7.15 (7.25)
Thrombocytopenia at the time of bleeding (Plt <150)	7 (23.3%)
Clinical Presentation	
Melena	**24 (80)***
Hematochezia	5 (16.7)
Hematemesis	5 (16.7)
Etiology of Bleeding	
Clean based gastric ulcers	**13 (43.3)***
Clean based duodenal ulcers	3 (10.0)
Gastric ulcer with visible vessel	3 (10.0)
Duodenal ulcer with visible vessel	2 (6.7)
Esophagitis/Gastritis/Duodenitis	**16 (53.3)***
Dieulafoy	2 (6.7)
Gastric AVMs	2 (6.7)
Interventions	**13 (44.3)***
APC	1 (3.3)
Bicap cautery	2 (6.7)
Endoclip	8 (26.6)
APC + Epinephrine Injection	1 (3.3)
Endoclip + GDA embolization	1 (3.3)
Overall severe complications	**3 (10)***
Uncontrollable bleeding	1(3.3%)
Death	2(6.7%)

Table 2: Univariant analysis of baseline characteristics of cancer patients exposed to ICIs

Variable	Non-Bleeding (n=90)	Bleeding (n=30)	p-value
Age, mean ± SD	70.6 ± 11.0	69.6 ± 11.3	0.6854
Gender (Male), n (%)	56 (62.2)	19 (63.3)	0.9133
Race (White), n (%)	76 (84.4)	23 (76.7)	0.3316
Hispanic, n (%)	1 (1.1)	2 (6.7)	0.1539
1ST MED type, n (%)			0.0010
Pembrolizumab	41 (45.6)	24 (80.0)	
Other	49 (54.4)	6 (20.0)	
BMI, n (%)			0.0203
< 26	38 (42.2)	20 (66.7)	
≥ 26	52 (57.8)	10 (33.3)	
History of Upper GI Bleed, n (%)	7 (7.8)	0 (0.0)	0.1902
On Aspirin prior to procedure, n (%)	5 (5.6)	12 (40.0)	<0.0001
On Plavix prior to procedure, n (%)	1 (1.1)	1 (3.3)	0.4391
On Warfarin prior to procedure, n (%)	0 (0.0)	1 (3.3)	0.2500
CKD, n (%)	34 (37.8)	13 (43.3)	0.5893
DM, n (%)	33 (36.7)	9 (30.0)	0.5073
Cirrhosis, n (%)	4 (4.4)	1 (3.3)	1.0000
Type of cancer treated, n (%)			0.0253
Non-small cell lung cancer	25 (27.8)	15 (50.0)	
Other	65 (72.2)	15 (50.0)	
ICPI induced side effect, n (%)	25 (27.8)	16 (53.3)	0.0106
Treatment with steroids, n (%)	21 (23.3)	11 (36.7)	0.1527
Treatment with Infliximab or Entyvio, n (%)	1 (1.1)	1 (3.3)	0.4391
Current alive, n (%)	29 (32.2)	8 (26.7)	0.5682
PPI, n (%)			0.8307
No	53 (58.9)	17 (56.7)	
Yes	37 (41.1)	13 (43.3)	

Results

- The most common endoscopic findings were esophagitis/gastritis/duodenitis (Table 1)
- 44.3% (n=13) of patients in the bleeding group required intervention (Table 1)
- Compared with the non-bleeding cohort, patients who developed UGIB bleeding had lower BMI (p= 0.0203) (Table 2)
- Non-small cell lung cancer was the most frequently treated malignancy in the bleeding group (Table 2)
- Patients in the bleeding group had higher exposure to pembrolizumab compared to the non-bleeding group (80% vs. 45.6%, p= 0.001) (Table 2)
- The incidence of other IrAE were more frequent in the bleeding group compared to the non-bleeding cohort (53.5% vs. 27.8%, p= 0.0106) (Table 2)
- The presence of other comorbidities (cirrhosis, diabetes and chronic kidney disease) were similar in both groups (Table 2)
- No difference in exposure to steroids and PPI prophylaxis between both groups (Table 2)
- On the multivariant analysis, exposure to pembrolizumab, aspirin and history of other irAE were predictive factors in development of bleeding (OR=3.66 p=0.0108)

Discussion

- This is a novel study that evaluates the risk of UGIB in cancer patients treated with ICIs
- In this univariate and multivariate analysis, exposure to aspirin, pembrolizumab and overall incidence of IrAEs were associated with increased risk of bleeding.