Impact of immunosuppression on cancer outcome after immune checkpoint inhibitors

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Introduction

Immune checkpoint inhibitors (ICIs) are becoming a staple in the management of certain cancer types but may give rise to immune-related adverse events (irAEs). Gastrointestinal (GI) irAEs may necessitate extended periods of steroid and biologic agent use which can put the patient at risk of developing infections and steroid-related complications. Moreover, the effect of immunosuppression on cancer outcomes in patients on immunotherapy is still understudied. In this study we aim to explore the impact of immunosuppression use on progression-free survival (PFS).

Methods

This was a retrospective, single center study. All patients treated with ICI who developed GI irAEs within one year of ICI initiation were included; patients who received non-ICI chemotherapy within the study window after termination of immunotherapy were excluded. The study window ranged from May 2011 to June 2020. Information regarding steroid use was collected. Data was analyzed using SPSS 26.0. Continuous variables were described using the median and interquartile range, categorical variables were defined by their count and frequency. Chi-square tests were used to explore the relationship between immunosuppression and cancer progression as well as steroid-related complications. COX Hazard analysis was conducted to evaluate progression-free survival. Univariate logistic regression was used to select the variables included in the model. A duration of steroid treatment of 30 days was the cut-off used to differentiate between short and long-term steroid use for analysis.

Results

A total of 116 patients were included in this study. 54.3% of the sample was male, and 95.3% were white with a median age of 60 (52-70). The majority of patients had melanoma (63.0%), and patients most commonly received PD-1/L1 inhibitors (44.9%) or combination ICI therapy (32.3%). All patient included in this study developed IMDC, though 15 patients had no colitis symptoms (only diarrhea).

Results

Of the 116 patients included, 49 patients received no immunosuppression, 23 received a short duration of steroids + biologics, and 44 received long durations of immunosuppression for colitis within the study interval. We found that development of colitis and shorter durations of steroid use for colitis were associated with less cancer progression by the fourth staging. Immunosuppression was associated with less cancer progression by third staging. 57.1% of patients on steroid treatment developed complications, most commonly psychologic disturbances (44%), metabolic disorders (23.5%), and infection (5%). Longer durations of steroids with (p=0.022) and without (p=0.019) biologics were associated with a higher risk of steroid-related complications than shorter durations.

Table 1: Progression across staging among different groups

	No. (%)			
	Progression by first staging	Progression by second staging	Progression by third staging	Progression by fourth staging
Colitis n=101	8(18.2%)	11(16.2%)	21(24.7%)	27(26.7%)
No colitis n=15	3(27.3%)	5(28.5%)	8(61.5%)	8(53.3%)
p-value	0.674	0.120	0.018	0.036
Immunosuppression n=68	5(15.2%)	7(14.3%)	13(22.0%)	15(22.1%)
No immunosuppression n=48	6(28.6%)	9(30.0%)	16(42.1%)	18(36.7%)
p-value	0.233	0.092	0.035	0.082
No immunosuppression n=49	6(28.6%)	9(30.0%)	16(42.1%)	18(36.7%)
Short duration steroids n=23	1(9.1%)	1(6.3%)	2(11.8%)	2(8.7%)
Long duration steroids n=44	4(20.0%)	5(16.1%)	9(22.5%)	11(26.8%)
p-value	0.434	0.127	0.039	0.045

Figure 1: Progression-free survival curve for different steroid duration groups

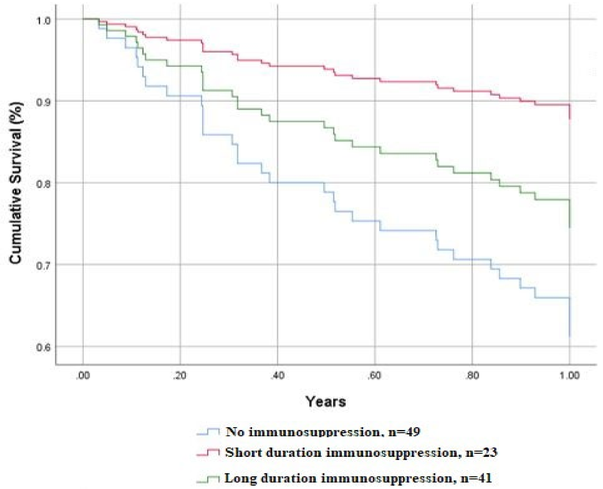

Table 2. Multivariate Cox model for progression-free survival (one year follow up)

Parameter	Hazard ratio (95% CJ)	P
Colitis grade 3-4 vs. 1-2	0.9(0.3-2.8)	0.954
Number of ICI infusions	0.9(0.9-1.0)	0.089
Short duration Steroid+Biologics vs. No immunosuppression	0.3(0.1-0.9)	0.048
Long duration Steroid+Biologics vs. No immunosuppression	0.6(0.3-1.3)	0.223
Short duration vs. long duration steroid+biologic	0.4(0.1-1.6)	0.216

Table 3. Complication rates among different steroid durations

	Short steroid duration	Long steroid duration	Long steroid/biologic duration
No complications	10(76.9%)[a,b]	22(40.7%)[a]	9(32.1%)[b]
Complications	3(23.1%)[c,d]	32(59.3%)[c]	19(67.9%)[d]

Footnote: Columns with the same superscript were significantly different at the p>0.005 level. [b,d] p=0.022; [a,c] p=0.019
There was no significant difference between long term steroid use with and without biologic agents.

Discussion

Our study explored the relationship between colitis, immunosuppression, and cancer outcomes. We found that the development of colitis after ICI was associated with less cancer progression by the fourth staging, as was a shorter duration of steroid use to treat the initial colitis episode. In this cohort, there was an effect of immunosuppression for colitis on progression-free survival. Finally, longer steroid treatment regimens were associated with a higher risk of complications including but not limited to psychologic disturbances (anxiety, agitation, psychosis, etc), metabolic disturbances (hyperglycemia, diabetes, weight gain, etc) and infections. The finding that colitis was associated with less cancer progression is similar to what has already been shown in the literature – the development of colitis likely reflects an enhanced immune response resulting from ICIs, suggesting that the immunotherapy is being effective. On the other hand, the role of immunosuppression in cancer outcome has not been established, and the findings in the literature are inconsistent. Since ICIs function by stimulating the patient's immune system allowing it to target cancer cells more effectively, the immunosuppression induced by steroids would theoretically hinder the efficacy of immunotherapy and lead to worse cancer outcomes. Currently, the results are mixed, with some studies showing a deleterious effect of steroids while others show no effect. Further studies are needed to clarify the impact of steroid therapy on cancer and immunotherapy outcomes.

Conclusions

To conclude, our study found that shorter durations of immunosuppression for colitis lead to better progression-free survival at one year for these patients. Immunosuppression overall, however, had no effect on PFS. That said, given the high risk of complications from steroid use and the uncertain relationship between steroid use and cancer outcome, further studies are critical to evaluate the safety of long-term immunosuppressive regimens in managing immunotherapy toxicities.

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