Correlation of Serum Iron Level and Duration of Response to Ipilimumab and Nivolumab in Metastatic Clear Cell Renal Carcinoma (mccRCC)

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Introduction

Combination ipilimumab + nivolumab (ipi+nivo) is one recommended combination immune therapy for treatment of intermediate-poor risk patients. Durable responses are observed in some patients. However approximately 20% of patients do not respond to this treatment. There are no predictive biomarkers for this treatment representing an unmet clinical need (1). Iron consumption contributes to disease progression through the HIF pathways, and may also be consumed by tumor associated macrophages (TAM) in the tumor microenvironment contributing to progression (2). We hypothesize that low serum iron may be predictive of poor response to ipi+nivo therapy.

Methods

Study Design

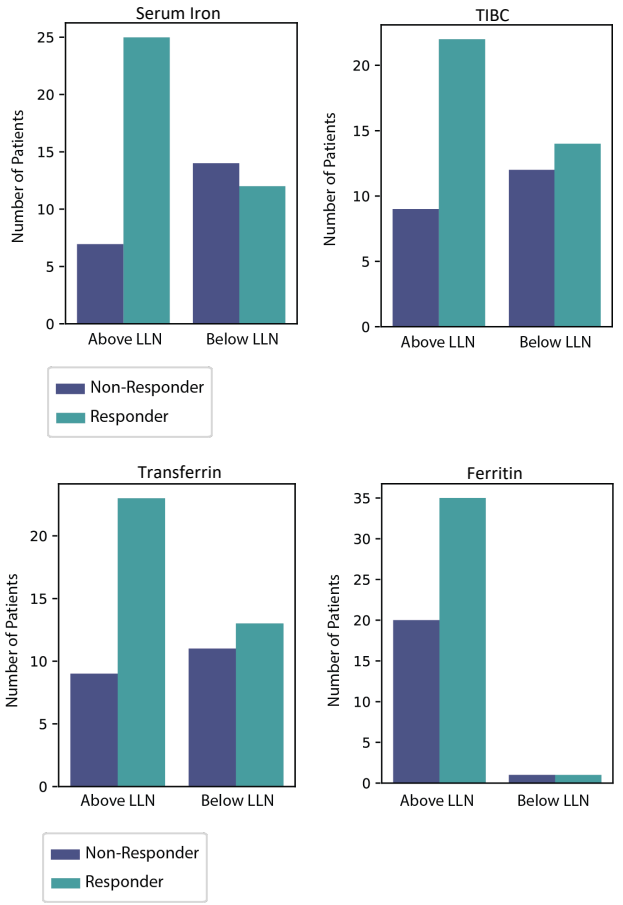
In this IRB approved study, patients with mccRCC treated with ipi/nivo were retrospectively identified from databases at the Huntsman Cancer Institute and the University of Iowa. Patients must have had serum iron labs drawn prior to the start of ipi/nivo or up to 1 month after initiation. Patients could have received ipi/nivo in any line. The primary endpoint is the duration of response correlated with serum iron levels. Patients were categorized as either having low serum iron levels or normal serum iron levels. Secondary endpoints included response correlated to other iron indices: total iron binding capacity (TIBC), ferritin and transferrin. Duration of response was defined as the time from initiation of ipi/nivo to the time of discontinuation or death. Responders were considered those who had a duration of treatment >4 months, while non-responders were those with a treatment <4 months. Statistical significance was determined by chi-squared test.

Patient Characteristics

81 patients in total were included between both centers. 69 (85.2%) treated at HCI and 12 (14.8%) treated at Iowa. Patients were treated between December 2013 and June 2021. 36 (44.4%) of patients were treated in the first-line. In total 7 (8.6%), 61 (75.3%), 13 (16%) of patients had IMDC favorable, intermediate, and poor risk disease respectively. 53 (65.4%) of patients had normal serum iron and 28 (34.6%) of patients had low serum iron.

Results

Characteristic	Number (Percentage)/ Mean
Sex	
Male	71.7% (58)
Female	28.4% (23)
IMDC Risk	
Favorable	8.6% (7)
Intermediate	75.3% (61)
Poor	16% (13)
Race	
White Non-Hispanic	88.9% (72)
Asian	2.5% (2)
Hispanic	2.5% (2)
American Indian/Alaskan Native	2.5% (2)
Line of Therapy	
1	44.4% (36)
2	28.4% (23)
3	13.6% (11)
4	11.1% (9)
5+	2.5% (2)
Age	61.17
BMI	29.33



Results

Patients with serum iron below lower level normal (LLN) had a response rate of 46.15% while patients with serum iron above LLN had a response rate of 78.125% (n=58, p=0.012). Patients with ferritin below (51) and above (2) LLN had a response rate of 62.7% and 50% respectively (n=53, p=0.715). Patients with TIBC below (25) and above (33) LLN had a response rate of 52% and 72.7% respectively (n=58, p=0.104). Patients with transferrin below (26) and above (31) LLN had a response rate of 53.8% and 71.0% respectively (n=57, p=0.182).

Conclusions

In this cohort of patients a low serum iron was associated with improved likelihood of a clinical benefit from ipi/nivo compared to patients with a normal/high serum iron. Ferritin, transferrin and TIBC were not predictive of a clinical response. This is a hypothesis generating, retrospective study. Therefore these results need to be verified in future prospective studies or validated in banked samples of already conducted phase III clinical trials.

Limitations

Because of the current dataset size limitations, this study is currently only hypothesis generating. The study is also limited to response to ipi/nivo rather than evaluating these in conjunction with other immune therapy combinations. It is also possible that serum iron serves biomarker of aggressive disease biology rather than a pure marker of immune response. Further studies should evaluate both different combinations of immune therapies, as well as clarifying if the tumor iron consumption may be connected with alternate mechanisms of action of immune therapies.

References

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