Original Investigation

Dorsal Muscle Attenuation May Predict Failure to Respond to Interleukin-2 Therapy in Metastatic Renal Cell Carcinoma

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Rationale and Objectives: To explore whether the sarcopenia body type can help predict response to interleukin-2 (IL-2) therapy in metastatic renal cell carcinoma (RCC).

Materials and Methods: Institutional review board approval was obtained for this Health Insurance Portability and Accountability Act-compliant retrospective cohort study of 75 subjects with metastatic RCC who underwent pretreatment contrast-enhanced computed tomography within 1 year of initiating IL-2 therapy. Cross-sectional area and attenuation of normal-density (31–100 Hounsfield units [HU]) and low-density (0–30 HU) dorsal muscles were obtained at the T11 vertebral level. The primary outcome was partial or complete response to IL-2 using RECIST 1.1 criteria at 6 weeks. A conditional inference tree was used to determine an optimal HU cutoff for predicting outcome. Bonferroni-adjusted multivariate logistic regression was conducted to investigate the independent associations between imaging features and response after controlling for demographics, doses of IL-2, and RCC prognostic scales (eg, Heng and the Memorial Sloan Kettering Cancer Center [MSKCC]).

Results: Most subjects had intermediate prognosis by Heng (65% [49 of 75]) and the MSKCC (63% [47 of 75]) criteria; 7% had complete response and 12% had partial response. Mean attenuation of low-density dorsal muscles was a significant univariate predictor of IL-2 response after Bonferroni correction ($P = 0.03$). The odds of responding to treatment were 5.8 times higher for subjects with higher-attenuation low-density dorsal muscles (optimal cutoff: 18.1 HU). This persisted in multivariate analysis ($P = 0.02$). Body mass index ($P = 0.67$) and the Heng ($P = 0.22$) and MSKCC ($P = 0.08$) clinical prognostic scales were not significant predictors of response.

Conclusions: Mean cross-sectional attenuation of low-density dorsal muscles (ie, sarcopenia) may predict IL-2 response in metastatic RCC. Clinical variables are poor predictors of response.

Key Words: Morphometry; sarcopenia; interleukin-2; metastatic renal cell carcinoma; response prediction.

INTRODUCTION

Sarcopenia is a recently explored body type (1–17) that is diagnosable by data routinely acquired with computed tomography (CT) and is associated with a range of negative outcomes including the following: postoperative infectious and noninfectious complications (2–7), mortality following liver transplantation (3), adrenocortical carcinoma mortality (8), and truncated disease-free survival in stage III melanoma managed with systemic interleukin-2 (IL-2) (9), among others (10–17). In short, sarcopenia is the combination of low core muscle volume and density—characterized by diminutive psoas and dorsal muscles—and high core muscle adiposity. Sarcopenia has been shown repeatedly to outperform common clinical markers of general health such as age and body mass index in predicting patient outcomes (1–17).

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Sarcopenia has been shown to be prognostic in stage III melanoma (9) and predictive of response to ipilimumab in stage IV melanoma (16). We were interested to know whether the sarcopenia body type also could be used to predict outcome in patients with metastatic renal cell carcinoma (RCC) treated with IL-2, as both melanoma and RCC are responsive to immunotherapies (18–23). A small subset (7%–8%) of patients with metastatic RCC treated with IL-2 experience a complete response to therapy that tends to be durable (18), with some patients alive and without disease for more than 10 years. However, the majority of patients do not respond at all, and reliable pretreatment prediction of which patients are most likely to benefit using clinical criteria has been elusive. Because of the high cost, potential toxicity, and low response rate (~20%) associated with IL-2 therapy, sparing patients from therapy who are least likely to benefit is desirable (21).

The purpose of this study was to explore whether the sarcopenia body type can help predict response to IL-2 therapy in metastatic RCC.

METHODS

Institutional review board approval was obtained for this Health Insurance Portability and Accountability Act-compliant retrospective cohort study.

Subjects

All patients who underwent systemic IL-2 therapy for treatment of metastatic RCC at the study institution from 2000 to 2014 were identified using an existing prospective institutional cancer registry ($n = 215$). Inclusion criteria were metastatic RCC treated with systemic IL-2, pretreatment contrast-enhanced CT of the chest and/or abdomen performed within 1 year of CT, imaging data recoverable from the institutional picture archiving and communications system (PACS), and imaging that includes the T11 vertebral body. There were 76 subjects who met all inclusion criteria. One subject was excluded because of metallic hardware at the T11 level. There were no other exclusion criteria. One pre-IL-2 baseline CT scan ($n = 75$) was analyzed for each subject ($n = 75$). The study population details are shown in Table 1.

Imaging and Patient-Level Data

Details pertaining to the index contrast-enhanced CT, demographic data, performance status, comorbid diseases, burden and type of metastatic disease, histologic grade of the primary RCC, and IL-2 treatment regimen were recorded for each subject (Tables 1 and 2). This information was gathered from the institutional cancer registry, the Digital Imaging and Communications in Medicine (DICOM) headers associated with each CT examination, and a review of the institutional electronic medical record system. Collection of these data was performed by multiple study authors.

TABLE 1. Patient Demographic Data

Characteristic	All Subjects ($n = 75$)
Median age (years)	54 (IQR: 50–58)
Male	51 (67%)
Body mass index (kg/m^2)	29 (IQR: 26–33)
Systemic therapy prior to IL-2 (all single agent)	8 (11%)
Days from RCC diagnosis to first IL-2	12 (IQR: 4–45)
Days from CT to first IL-2 dose	24 (IQR: 12–35)
Total IL-2 doses out of 28 possible	13 (IQR: 10–16)
Response at 6 weeks by RECIST 1.1	
Any response	14 (19%)
Complete response	5 (7%)
Partial response	9 (12%)
Progression	40 (53%)
Stable disease	21 (28%)
Overall subject health	
Karnofsky performance status	100 (IQR: 90–100)
Charlson comorbidity index	8 (IQR: 8–9)
RCC Fuhrman nuclear grade	3 (IQR: 3–4)
Distribution of metastatic disease	
Lung	65 (87%)
Liver	12 (16%)
Renal/nephrectomy bed	22 (29%)
Adrenal	11 (14%)
Other abdominal	13 (17%)
Bone	13 (17%)
Central nervous system	1 (1%)
Other nonabdominal	5 (7%)
MSKCC prognostic score	
High (worst prognosis)	3 (4%)
Intermediate	47 (63%)
Low (best prognosis)	25 (33%)
Heng prognostic score	
High (worst prognosis)	6 (8%)
Intermediate	50 (66%)
Low (best prognosis)	19 (26%)

CT, computed tomography; IL-2, interleukin-2; MSKCC, Sloan Kettering Cancer Center; RCC, renal cell carcinoma; RECIST, Response Evaluation in Solid Tumors.
Continuous variables are presented as medians and interquartile ranges (IQR).

Interleukin-2 Therapy

All subjects underwent a pretreatment evaluation including a possible dobutamine stress echocardiogram, staging CT scans, and CT or magnetic resonance imaging of the central nervous system. High-dose IL-2 was administered intravenously at a standard dose of 600,000 international units (IU) over 15 minutes every 8 hours for up to 14 doses each cycle for two cycles 9 days apart (18). The administration of individual doses was per the clinical judgment of one of two treating expert medical oncologists based on clinical parameters including hemodynamic stability and toxicities. Supportive measures such as intravenous crystalloids, nonsteroidal anti-inflammatory agents, loperamide, acetaminophen, and dopamine as needed for renal