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TO THE EDITOR: Significant progress in systemic therapy of metastatic renal cell carcinoma (mRCC) has been made over the last 5 years, with a plethora of targeted agents currently approved in different clinical settings. However, not all mRCC patients respond to treatment with these drugs and currently there are no validated biomarkers to predict clinical outcome. We therefore read with interest Armstrong et al's[1] report of the prognostic and predictive significance of baseline serum lactate dehydrogenase (LDH) in patients with intermediate- and-poor risk mRCC treated in a first-line trial of the mammalian target of rapamycin (mTOR) inhibitor temsirolimus, interferon-alfa, or both in combination. As expected, in multivariate analysis, overall survival (OS) was significantly shorter in patients with LDH more than 1× the upper limit of normal (ULN) compared with patients with LDH ≤ 1 × ULN at baseline. The importance of a high baseline LDH as a predictor of response to temsirolimus was also examined: in patients with LDH more than ULN, median OS with temsirolimus was 6.9 months versus 4.2 months with interferon-alfa (hazard ratio, 0.56; 95% CI, 0.38 to 0.81; $P = .002$). There was no difference in risk of death between temsirolimus and interferon-alfa treatment in patients with normal LDH. However, patients with an elevated LDH in this trial were more likely to be of poor risk by Motzer criteria and it is unlikely that interferon-alfa provided any benefit in this group[2] and, given the associated toxicity, it may even have been detrimental. Survival comparisons between temsirolimus and interferon-alfa should therefore be viewed with caution.

The prognostic impact of baseline LDH was evaluated in the RECORD-1(Renal Cell Cancer Treatment With Oral RAD001 Given Daily) trial of the mTOR inhibitor everolimus in mRCC refractory to anti–vascular endothelial growth factor (VEGF) therapy.[3] High LDH was found to be prognostic for OS, but not progression free survival (PFS) in univariate analysis, but it was not included in the final model of multivariate analysis because of its nonlinear effect. High pretreatment LDH is however a prognostic marker for both PFS and OS in the first-line setting during treatment with the VEGF receptor tyrosine kinase inhibitor sunitinib and interferon-alfa in predominantly good or intermediate risk (93%) mRCC[4] as well as for OS in the sunitinib-refractory setting during treatment with the VEGF receptor tyrosine kinase inhibitor axitinib.[5] To examine further the relationship between prognosis and LDH during everolimus therapy, we evaluated all patients with mRCC from our institutional database treated with inhibitor everolimus (n = 57) after failure of prior anti-VEGF therapy. The majority of patients (78%) were of good or intermediate risk. We found a high baseline LDH to be prognostic for OS, similar to Armstrong et al's results[1]; the median OS of patients with a normal LDH in our series was 8.6 months compared with 6.2 months for those with an LDH of more than ULN (hazard ratio, 1.71; 95% CI, 0.99 to 2.96; log-rank $P = .05$). We could not evaluate the predictive effect of baseline LDH owing to a lack of a comparator arm; the retrospective nature and small single-institution sample size are limitations of this analysis.

Finally, hypertension is commonly associated with anti-VEGF therapy and appears to be a class effect. The incidence of all-grade hypertension ranges between 22% and 55% in various studies with these agents.[6-10] Data suggest that hypertension secondary to treatment with sunitinib is associated with improvement in clinical outcomes (objective response rate, PFS, and OS)[11] and similar results have been observed with other anti-VEGF agents.[12,13] mTOR inhibitors may also have antiangiogenic activity,[14] and treatment-emergent hypertension has been observed as a consequence of treatment with non-VEGF therapy (eg, cytotoxic agents in non–small-lung cancer in which it has been found to be prognostic but not predictive of differential outcome).[15] Therefore, it would be interesting to know from the data set reported by Armstrong et al[1] whether the development of hypertension correlated with survival on therapy or correlated with baseline LDH.

In conclusion, the results of the study by Armstrong et al[1] are encouraging and indicate progress toward predicting the clinical outcome of mRCC patients treated with a targeted agent. However, further corroboration of these findings is needed to establish their relevance for clinical practice.

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