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Letter to the Editor

Long-term survival in a case of metastatic papillary renal cell carcinoma

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Dear Editor,

The papillary subtype of renal cell carcinoma (pRCC) has a poorer prognosis when compared to their more common clear cell counterpart RCC (ccRCC). We wish to report a case of metastatic pRCC who has an ongoing response to sunitinib for 58 months.

A 25-year-old Omani female presented in December 2009 with right flank pain. There was no hematuria or systemic features, or family history of cancer. Clinically, she was in performance status (PS) 1 (WHO). Laboratory investigations were normal. CT scan of chest/abdomen [Figure 1] and MRI of abdomen revealed a 7.5 cm × 7.3 cm × 7.2 cm right renal mass, without significant abdominal lymphadenopathy, a normal

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left kidney and adrenals, normal inferior vena cava without thrombi, and multiple liver lesions involving both lobes. She underwent right radical nephrectomy on 19 January 2010. Histopathology was consistent with pRCC type; per operative liver biopsy also showed metastatic pRCC. The tumor was vimentin positive, panCK positive, WT1 negative, Ker7 negative, and CD10 negative.

She was started on sunitinib on 13 March 2010 at the standard schedule. On her first review in April 2010, she was noted to have grade 2 rash over her face, both arms, and abdomen needing dose reduction. CT-scan done in July 2010 showed a mixed response. Sunitinib dose was raised, but hypothyroidism was detected in October 2010, and dose was again reduced.

In March 2011, she developed diarrhea, mouth ulcers, hematuria, and hemorrhagic conjunctivitis with thrombocytopenia. Sunitinib was stopped and after recovery in April 2011, restarted at 50 mg OD every other day (EOD). She developed skin rash and thrombocytopenia when an attempt was made to increase

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the dose, and so she was placed on a schedule of 50 mg EOD 4 weeks on, 2 weeks off from July 2011.

MRI of liver in September 2012 [Figure 2] revealed regression of liver lesions with areas of obvious enhancement along with focal areas of parenchymal hemorrhage, denoting activity. CT-scan in February 2014 showed stable disease. In her last review in June 2014, she was in PS 0 (WHO), weight 58 kg (up from 41 kg), with normal clinical and laboratory findings.

Papillary RCC (pRCC) is the second most common subtype comprising 10-15% of kidney cancers. Histologically, it can be divided into types 1 and 2 with different underlying genetic changes (in MET and fumarate dehydrogenase genes); type 2 has a poorer prognosis.

In Motzer *et al*. series of 18 metastatic pRCC patients, the median survival was 5.5 months, and no patient survived beyond 2 years.[1] The International Metastatic RCC Database Consortium (IMDC) analysis of 2215 patients from 20 centers showed that overall survival is approximately half in non-ccRCC as compared to ccRCC (12.8 vs. 22.3 months).[2] A study of 4941 patients from Germany showed, quite paradoxically that pRCC had a good prognosis if localized (HR 0.45) but poor if metastatic (HR 1.47).[3]

It is recognized that some drug-induced adverse events such as rash, hypothyroidism, and hypertension may act as surrogate markers of a drug's clinical activity, and may be predictive of treatment outcomes. Our patient developed skin rash and sub-clinical hypothyroidism; however, she did not develop hypertension.

Our patient is a long-term responder with stable demonstrable lesions in the liver; they are usually (>90%) of ccRCC subtype.[4] She is in good risk category by the IMDC (Heng) prognostic model.[2] Prolonged response to specific targeted therapy suggests that the tumor is "addicted" to a particular oncogene/pathway. Sunitinib, in addition to vascular endothelial growth factor receptor (VEGFR) inhibition, has an inhibitory effect on other genes/products such as KIT, FLT-3, and platelet-derived growth factor receptor (PDGFR)-alpha and PDGFR-beta. PDGFR-alpha overexpression has been found in pRCC but not it's sensitizing mutations. However, c-KIT cytoplasmic expression by immunohistochemistry (IHC) and a point mutation at intron 17 (T>A) has been reported in 94% of pRCC (17/18 cases studied by polymerase chain reaction and direct DNA sequencing);[5] it is possible that our case has the same or a similar mutation. Unfortunately, specific mutation studies could not be done. Phenotypically, she does not fit into a familial cancer syndrome, and we can only speculate at the underlying mutation that conferred such prolonged sensitivity to sunitinib. Such "exceptional responders" provide a remarkable opportunity for drug development of the P2G (phenotype to genotype) model.[6]

We report a case of metastatic pRCC on sunitinib with stable disease at 58 months; studies of such patients will be useful in detecting new molecular targets that will improve the outcomes in these, otherwise poor prognosis cases.

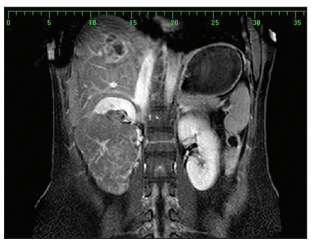

Figure 1: Magnetic resonance imaging - abdomen (December 2009)

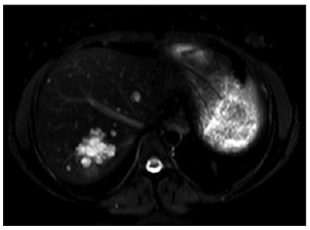

Figure 2: Magnetic resonance imaging - abdomen (September 2012)

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Conflicts of interest

There are no conflicts of interest.

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