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Commentary

Predicting Molecular Models: Where Are We Going?

Raffaele Ratta, Elena Verzoni, Paolo Grassi, Monica Niger, Giuseppe Procopio*

Medical Oncology I, Genitourinary Unit, Fondazione IRSCC Istituto Nazionale dei Tumori, Via Venezian 1, 20133 Milan (Italy)

Kidney cancer is the seventh most common site for tumors, with 350,000 new cases diagnosed in 2013 worldwide and is associated with more than 140,000 deaths per year. In the USA, 61,560 new cases are estimated in 2015 (Ferlay et al., 2013; Capitanio and Montorsi, 2015). Despite several advances, about 30% of patients have a metastatic disease at diagnosis (Gupta et al., 2008) and another 30% of patients will have a relapse after nephrectomy and will become metastatic during follow-up (Athar and Gentile, 2008). Risk group stratification is useful to optimize treatment decisions and maximize patient survival.

In this issue of *EBioMedicine* (Kim et al., 2015), Hyung Lae Kim and colleagues have described an 8-gene model of overall survival (OS) using primary untreated renal cell carcinoma (RCC) formalin-fixed, paraffin-embedded specimens collected for Cancer and Leukemia Group B (CALGB) 90206 trial, which was a randomized phase III, open label study comparing bevacizumab plus interferon alpha (IFN) versus IFN alone (Rini et al., 2010). The CALGB 90206 trial has demonstrated a benefit, in terms of progression-free survival (PFS), in favor of the combination therapy (median PFS 8.5 vs 5.2 months, $p < 0.0001$), but no OS benefit (median 17.4 and 18.3 months in monotherapy and combination therapy arm respectively, $p = .097$). Patients included in the study had a metastatic or unresectable clear cell renal cell carcinoma; 353 tumor samples have been analyzed, but 29 of them have failed quality control. The final analysis of clinical outcome was based on 324 patients, which have been stratified according to the Memorial Sloan–Kettering Cancer Center (MSKCC) risk factors, the only clinical variable included in the final multivariable model.

By using a RT-qPCR, the authors measured 424 candidate genes, identifying 21 prognostic genes with a q-value <0.05 that were selected for the multivariate analysis that has lead to the identification of 8 genes predicting OS. The final prognostic model described includes polybromo 1 (PBRM1) related genes (which is the second most important gene in RCC with Von Hippel–Lindau related genes—VHL), whose functions are involved with cancer progression such as: CEP55, PCNA, CDK1 (involved in proliferation), TRAF2 (involved in apoptosis), CRYL1, HSD17B10 (involved in metabolism), and HGF (involved in invasion) (http://www.ncbi.nlm.nih.gov/gene, n.d.; Tun et al., 2010). This experience has shown that decreasing levels of CRYL1, PCNA and CDK1 are associated with a worse OS, while the expression of TRAF2, USP6NL, CEP55, HGF and HSD17B10 has an inverse association.

For the first time, this study identifies a multimarker prognostic signature in a multicenter, phase III trial on mRCC. A first advantage of extrapolating data from a large multicenter study, as the authors state, is that it is less vulnerable to bias introduced by the single institution procedures about tissue handling and storage. Another strong point of this study is that, while other biomarker studies also included patients with localized and non-metastatic RCC, Kim and colleagues' study includes only advanced disease, permitting a more practice clinical application in a group of patients in which RCC is associated with a bad prognosis. The methods used to identify genes, based on real-time PCR, are routinely performed by many hospitals and laboratories and they are highly reproducible and usually inexpensive in clinical practice, making the study very interesting in the identification of predicting and prognostic factors in RCC. Although Kim and colleagues' study is very extensive and well described, the main limitation is the lack of an external validation cohort.

The study is a good example of molecular research; it highlights the need for identification of prognostic factors and predictive ones and provides new molecular targets. The originality of this paper is the identification of a molecular multimarker prognostic signature in RCC, which supports the well known clinical prognostic factors.

These findings raise some points for further investigation. First, the identification of a model of genes predictive of OS in RCC, together with the best known MSKCC risk factor, could allow physicians to stratify and select patients for the best treatment strategies. These findings highlight the need for identifying new molecular predictive factors that can enhance clinical ones (which are largely available and solidly used in clinical practice). Second, it would be interesting to establish if the expression of a particular gene among those identified is a predictive factor of response or resistance to specific treatments. This will certainly guide treatment decisions. Third, methodology should be simple and standardized in order to be duplicated in a real-world unselected population. Finally, appropriately sized and rigorously evaluated prospective studies or prospectively collected external datasets would be useful to put this method and these findings into clinical practice.

Conflicts of Interest

The authors declared no conflicts of interest.

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* Corresponding author.
E-mail address: giuseppe.procopio@istitutotumori.mi.it (G. Procopio).

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