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Prognostic factors in advanced renal cell cancer

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ABSTRACT

The identification of reliable and reproducible prognostic factors (defined as those factors that define the risk of death, or of recurrence, independently of therapy) in advanced renal cell carcinoma patients has became a priority in this field. To date, the Memorial Sloan Kettering Cancer Center – or Motzer's – criteria are those more commonly used, especially within clinical trials, but their role in the era of molecularly-targeted therapies is challenged. Molecular and genetic factors are currently being studied – with still conflicting results –, trying to incorporate them into presently available score systems and algorithms. The next generation of prognostic tools will probably include both genomic and proteomic techniques.

1. Introduction

Despite the recent therapeutic improvements obtained with the use of molecularly-targeted agents,[1] metastatic renal cell carcinoma (RCC) should still be considered incurable.

This lack of curative treatment options, together with the peculiar (sometimes even bizarre) natural history of metastatic RCC, and the highly perceived problem of the costs of the newer agents (in a global situation characterised by a shortage of resources), highlights the need for identifying both prognostic and predictive factors in these patients. Prognostic factors, in particular, are those factors that define the risk of death (or of recurrence) independently of therapy; as such, they should help us to tailor specific treatment strategies for patients, provide them with informations about their prognosis and ensure proper comparability between patient populations enrolled into clinical trials, leading to a correct interpretation of the results reported.[2]

Even though already extensively studied in patients radically resected, prognostic factors have gained relevance also in the metastatic setting, where presently they are driving the selection of patients into clinical trials.

2. Prognostic factors: the past

Until recently, prognosis in RCC was mostly predicted by evaluating clinical and histopathological parameters, e.g. the tumour, nodes, metastases (TNM) stage, Fuhrman grade, performance status (PS).[3,4]

In a multivariate, retrospective, analysis of more than 600 patients enrolled into ECOG-sponsored trials performed in the late 1980s, Elson et al.[5] identified five indicators of survival: ECOG PS, time from initial diagnosis to treatment, number of metastatic sites, previous cytotoxic chemotherapy and recent weight loss; just counting the number of these factors, the authors were able to divide their patients into five prognostic groups, characterised by a completely different survival (12.8, 7.7, 5.3, 3.4, and 2.1 months, respectively).

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More recently, by analysing large numbers of patients, several Authors have generated a variety of models that have been, or are being, incorporated into clinical trials.

3. The memorial Sloan Kettering cancer center (MSKCC) – or Motzer's – criteria

Motzer and Colleagues, studying 670 advanced RCC patients treated with immunotherapy or chemotherapy, identified, using multivariate analysis, five pre-treatment features that were significantly associated with shorter survival: low Karnofsky PS (<80%), high LDH levels (>1.5 × ULN), low haemoglobin levels, high corrected calcium levels (>10 mg/dl) and the absence of nephrectomy.[6] Using these factors, they stratified patients into three groups (good-, intermediate- and poor-risk groups), endowed with a completely different prognosis; indeed, survival ranged from 20 months for patients from the good-prognosis group, to just 4 months for those in the poor-prognosis group.

A similar analysis was then applied to 400 patients treated with interferon-α as first-line systemic therapy; this analysis reduced the heterogeneity caused by multiple treatments and accounted for the essential role of cytoreductive nephrectomy in the metastatic setting in patients with good PS. Despite this, the prognostic model remained the same, except that time from diagnosis to treatment with interferon-α <1 year was substituted for the absence of previous nephrectomy.[7]

More recently, to analyse prognostic factors that would benefit modern day clinical trials, the same group reviewed clinical and laboratory data relative to 137 patients enrolled into clinical trials at MSKCC from 1990 onwards,[8] whose median overall survival was 12.7 months; independent predictors of worse survival were: poor Karnofsky PS (<80%), low haemoglobin (⩽13 g/dl in males, and 11.5 g/dl in females), and elevated corrected serum calcium (⩾10 mg/dl). Again, the number of poor prognostic variables stratified patients into favourable- (no risk factors), intermediate- (one risk factor) and poor-risk (two or three risk factors) groups. Favourable-, intermediate- and poor-risk groups were endowed by overall, 1- and 3-year survival rates of 76% and 25%, 49% and 11%, and 11% and 0%, respectively.

This model was externally validated in 353 patients treated on clinical trials at Cleveland Clinic,[9] where the investigators identified two additional independent prognostic factors, i.e. prior radiotherapy and number of metastatic sites.

Analysing patients enrolled into Sunitinib's registrative trial,[10] Motzer et al. developed a nomogram, first presented at 2007 ASCO annual meeting,[11] that proved able to predict the probability of being progression free at 12 months; the parameters used within this nomogram (which has predictive and not prognostic value, as defined above) were an evolution of the already mentioned MSKCC prognostic criteria, and included corrected calcium, number of metastatic sites, prior nephrectomy, thrombocytosis, time from diagnosis to treatment and LDH titres.

4. The University of California at Los Angeles (UCLA) integrated staging system

Zisman and Colleagues developed the so-called 'UCLA Integrated Staging System' (UISS) for both non-metastatic and metastatic patients, a system which integrated the 1997 TNM stage, ECOG PS, and Fuhrman grade.[12]

In an international multicentre study, however this algorithm proved not to be such accurate and reliable in metastatic patients as it was in patients with localised disease.[13]

5. Prognostic criteria in the era of molecularly targeted agents

All the above prognostic models and predictors of outcome were identified in patients who received immunotherapy, hormonal therapy, chemotherapy, a combination of the above or other non-molecularly targeted agents.

Thus, more recently, many Authors have addressed the issue of prognostic factors in the setting of molecularly-targeted (and especially VEGF-targeted) therapies.[14]

Choueiri et al. reported on the outcome of 120 patients with metastatic RCC treated with sorafenib, sunitinib, axitinib or bevacizumab; they identified five independent poor prognostic factors by multivariate analysis: time from diagnosis to current treatment <2 years, corrected serum calcium <8.5 mg/dl or >10 mg/dl, ECOG PS > 0, and baseline platelet and neutrophil count >300 K/ml and 4.5 K/ml, respectively. From these factors, three prognostic subgroups were identified, with a median PFS of 20.1, 13, and 3.9 months, respectively.[15] Interestingly, neither MSKCC criteria nor the Cleveland Clinic scores were associated with PFS in multivariate analysis.

Since the newer agents specifically target molecular pathways, such as the VEGF/VEGFR or the MAPK ones, proteins within this pathway have been screened for potential prognostic and/or predictive values.

A recent biomarkers analysis from the sorafenib registrative study showed that the phosphorylation status of ERK has no prognostic value and that, even though patients with baseline high VEGF levels had – as expected – a poorer prognosis, both high and low baseline VEGF groups benefited from sorafenib.[16]

Another recently reported biomarkers analysis from the phase II sunitinib trial in cytokine-refractory RCC patients found significantly larger changes in VEGF, soluble VEGFR-2 and -3 levels, in patients who yielded a partial response to treatment,[17] thus suggesting that baseline and/or changes in VEGF-related proteins could play a predictive (and possibly also a prognostic) role in the era of molecularly-targeted agents, a role that should nevertheless be confirmed by larger, prospective studies.

In view of the relevance of the Von Hippel-Lindau (VHL) gene in the molecular pathogenesis of RCC, VHL status has also been recently investigated. Choueiri et al. reported on the outcome of 123 patients treated with sunitinib, sorafenib, axitinib or bevacizumab;[18] patients with VHL inactivation responded better to the treatment (41% overall response rate [ORR] versus 31%) than patients with wild-type

VHL; moreover, a subgroup analysis showed that patients with loss of function mutations had a 51% ORR, compared with 31% in wild-type VHL carriers. In multivariate analysis, that included several other important clinical prognostic factors, the presence of a loss of function mutation remained an independent prognostic factor associated with improved response.

6. The future

Despite all the efforts made, to date the more reliable prognostic factors available for advanced RCC patients are still the MSKCC criteria, even though their role in the era of molecularly targeted agents is presently challenged, and they are not so commonly used in everyday's clinical practice.

The next generation of prognostic tools should incorporate the results of advancements in the fields of molecular biology and genetics. In particular, we do expect much from gene array techniques, which are able to screen for their differential expression of thousands of genes, and from protein expression analysis.[14]

Conflict of interest statement

Camillo Porta acted as a Consultant and/or a paid speaker for Bayer-Schering Pharma, Pfizer Oncology, Roche, Wyeth and Novartis Pharma. Ilaria Imarisio and Chiara Paglino acted as paid speakers for Bayer-Schering Pharma. Elisa Ferraris, Mario Mensi and Bruno Rovereto have nothing to disclose. This paper has not been supported by funding sources.

REFERENCES

1. Hutson TE, Figlin RA. Evolving role of novel targeted agents in renal cell carcinoma. *Oncology (Williston Park)* 2007;**21**:1175–80.
2. Park WH, Eisen T. Prognostic factors in renal cell cancer. *BJU Int* 2007;**99**:1277–81.
3. Ljunberg B. Prognostic markers in renal cell carcinoma. *Curr Opin Urol* 2007;**17**:303–8.
4. Lam JS, Klatte T, Kim HL, et al. Prognostic factors and selection for clinical studies of patients with kidney cancer. *Crit Rev Oncol Hematol* 2008;**65**:235–62.
5. Elson PJ, Witte RS, Trump DL. Prognostic features for survival in patients with recurrent or metastatic renal cell carcinoma. *Cancer Res* 1988;**48**:7310–3.
6. Motzer RJ, Mazumdar M, Bacik J, et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol* 1999;**17**:2530–40.
7. Motzer RJ, Mazumdar M, Bacik J, et al. Effect of cytokine therapy on survival for patients with advanced renal cell carcinoma. *J Clin Oncol* 2000;**18**:1928–35.
8. Motzer RJ, Bacik J, Schwartz LH, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. *J Clin Oncol* 2004;**22**:454–63.
9. Mekhail TM, Abou-Jawde RM, Boumerhi G, et al. Prognostic factors associated with long-term survival in previously untreated metastatic renal cell carcinoma. *J Clin Oncol* 2005;**23**:832–41.
10. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *New Engl J Med* 2007;**356**:115–24.
11. Motzer RJ, Figlin RA, Hutson TE, et al. Sunitinib versus interferon-alfa (IFN-α) as first-line treatment of metastatic renal cell carcinoma (mRCC): updated results and analysis of prognostic factors. *J Clin Oncol* 2007;**25**(Suppl.):5024 Abstract.
12. Zisman A, Pantuck AJ, Wieder J, et al. Risk group assessment and clinical outcome algorithm to predict the natural history of patients with surgically resected renal cell carcinoma. *J Clin Oncol* 2002;**20**:4559–66.
13. Patard JJ, Kim HL, Lam JS, et al. Use of the University of California Los Angeles integrated staging system to predict survival in renal cell carcinoma: an international multicenter study. *J Clin Oncol* 2004;**22**:3316–22.
14. Golshayan AR, Brick AJ, Choueiri TK. Predicting outcome to VEGF-targeted therapy in metastatic clear-cell renal cell carcinoma: data from recent studies. *Future Oncol* 2008;**4**:85–92.
15. Choueiri TK, Garcia JA, Elson P, et al. Clinical factors associated with outcome in patients with metastatic clear-cell renal cell carcinoma treated with vascular endothelial growth factor-targeted therapy. *Cancer* 2007;**110**:543–50.
16. Bukowski R, Heng D, Eisen T, et al. Sorafenib in advanced renal cell carcinoma (RCC): survival and biomarker results form a phase III trial. *Eur Urol* 2008;**7**(Suppl.):245. Abstract.
17. Deprimo SE, Bello CL, Smeraglia J, et al. Circulating protein biomarkers of pharmacodynamic activity of Sunitinib in patients with metastatic renal cell carcinoma: modulation of VEGF and VEGF-related proteins. *J Trans Med* 2007; **5**:32.
18. Choueiri TK, Vaziri SA, Rini BI, et al. Use of Von Hippel-Lindau (VHL) mutation status to predict objective response to vascular endothelial growth factor-targeted therapy in metastatic renal cell carcinoma. *J Clin Oncol* 2007;**25**(Suppl.):5012. Abstract.