Editorial Commentary

Single nucleotide polymorphisms in angiogenesis-related genes and outcomes from antiangiogenic therapies in renal cell carcinoma: really a step towards personalized oncology, or not at all?

Camillo Porta[1,2], Laura Cosmai[3], Mimma Rizzo[2], Mario Melazzini[4]

[1]Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy; [2]Division of Translational Oncology, I.R.C.C.S. Istituti Clinici Scientifici Maugeri, Pavia, Italy; [3]Division of Nephrology and Dialysis, A.S.S.T. Santi Paolo e Carlo, San Carlo Borromeo Hospital, Milan, Italy; [4]Scientific Direction, I.R.C.C.S. Istituti Clinici Scientifici Maugeri, Pavia, Italy

Correspondence to: Prof. Camillo Porta. Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy; Division of Translational Oncology, I.R.C.C.S. Istituti Clinici Scientifici Maugeri, via S. Maugeri 10, 27100 Pavia, Italy. Email: camillo.porta@icsmaugeri.it.

Provenance: This is an Invited article commissioned by Section Editor Xiao Li (Department of Urology, Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research & Nanjing Medical University Affiliated Cancer Hospital, Nanjing, China).

Comment on: George DJ, Martini JF, Staehler M, *et al.* Phase III Trial of Adjuvant Sunitinib in Patients with High-Risk Renal Cell Carcinoma: Exploratory Pharmacogenomic Analysis. Clin Cancer Res 2019;25:1165-73.

Submitted Jan 06, 2019. Accepted for publication Jan 21, 2019.
doi: 10.21037/atm.2019.01.51
View this article at: http://dx.doi.org/10.21037/atm.2019.01.51

By definition, single nucleotide polymorphisms (SNPs) are loci with alleles that differ at a single base level, with the rarer allele having a frequency of at least 1% in a random set of individuals within a given population (1).

Although the majority of these variations are silent, not altering any cellular function, some SNPs have been proved to contribute to the development of different diseases, including cancer, and to influence physiological responses to drugs, including anticancer agents.

Identifying which variations are involved in altering responses to anticancer agents could facilitate the development of a really personalized (or precise) approach to cancer patients; a genetic screening for specific SNPs in a person's genome could indeed be theoretically used to select drugs most appropriate for that individual, amplifying the likelihood of achieving a significant benefit, and reducing the risk of unwanted adverse events (AEs).

Recently, an exploratory analysis (2) evaluated the association between SNPs evidenced in several angiogenesis- or hypoxia-related genes, and the clinical outcomes of patients radically resected for a localized or locally-advanced renal cell carcinoma (RCC) who were treated with the anti-VEGFRs tyrosine kinase inhibitor (TKI) sunitinib within the already reported randomized, placebo-controlled, adjuvant phase III S-TRAC trial (3). In this study, correlations between SNPs in *VEGFR1*, *VEGFR2*, and *eNOS* genes and improved disease-free survival (DFS) in the sunitinib group compared with the placebo group were evidenced. Furthermore, SNPs in *VEGFR1*, *VEGFR2*, and *CCDC26* showed a potential trend toward prognostic value for either DFS or overall survival (OS) across the two treatment arms (2).

How this paper fills into available evidence?

Over the past 8 years, a number of different studies have addressed the potential effect on SNPs on different outcomes, including survival (either progression free survival—PFS, or OS), incidence of AEs, and dose reductions, in metastatic RCC (mRCC) patients treated with TKIs (though mainly sunitinib), overall yielding conflicting results, at best.

For example, a large study conducted in Sunitinib-treated mRCC patients, showed that most of the selected SNPs in angiogenesis-related genes were not associated with either survival or AEs (4), differently from what observed in other previous reports; only the *VEGFR1* rs9582036 SNP showed a statistically significant association with OS (4). Notably enough, the same *VEGFR1* rs9582036 SNP proved to be related to a shorter DFS with sunitinib within the S-TRAC

trial (2).

As a whole, the inconclusiveness of SNPs research in RCC was highlighted in a 2015 News and Views paper published on Nature Reviews Urology by Beuselinck and Zucman-Rossi, who asked themselves if the time for this kind of research was up (5). Indeed, commenting a large study in which previously observed associations between 22 SNPs in 10 genes and treatment outcome were investigated in 333 Sunitinib-treated mRCC patients (6), the Authors clearly evidenced that the vast majority of previously described associations were eventually not considered as validated (5).

However, the same Authors correctly noticed that plasma levels and efficacy or toxicity of TKIs are not entirely dependent on polymorphisms in genes involved in pharmacokinetics and pharmacodynamics, and thus claimed for further studies aimed at studying the influence of SNPs in mRCC (as well as other tumor types) treated with targeted agents (5).

Has something changed since the above News and Views paper? Is this research area really a potential step towards a personalized approach to cancer treatment? And finally, is this area still worth pursuing?

Let's start from the latter question.

The individual response to TKIs like sunitinib is highly variable; indeed, despite being treated with fixed doses of these agents—irrespective of parameters such as sex, age, and body surface area, a choice which, based on available data, could be considered not such a smart strategy (7)—some patients experience severe toxicity needing dose reductions, treatment interruptions or even the permanent discontinuation of treatment, whereas others show neither efficacy, nor toxicity.

Thus, the identification of specific SNPs in a patient's genome prior to the start of treatment (or even during its course) could help provide him/her with the most effective and the lowest toxic treatment, a condivisible but hypothetical statement which seems to confirm the need to further pursue the research in this field.

However, the level of inconclusiveness evidenced by Beuselinck and Zucman-Rossi (5) has not been improved in the past years; indeed, it is not a case that almost all published studies end with sentences such as "… *validation studies are needed* …", clearly leading to the conclusion—among the others—that SNPs research is presently not a right way towards personalized or precision Medicine.

Why this inconclusiveness?

In a recent paper by Ritchie and Van Steen (8), the Authors highlighted the fact that, as our technology improves, challenges in identifying clinically relevant genetic interactions also increase. The Authors summarized these challenges into three categories: abundance of methods, practical considerations, and biological interpretation.

The abundance of methods challenge refers not only to the present issue of which is the best suitable technology for conducting these studies, but also to the issue of the ideal material to study (e.g., formalin-fixed, paraffin embedded tissue) (9), as well as of the most appropriate statistical analysis needed to organize and interpret them; furthermore, from a very practical viewpoint a huge computational complexity arises when previous studies investigating small genomic regions have been replaced by studies covering the whole genome. Indeed, as highlighted by Ritchie and Van Steen "… *the number of combinations of interacting SNPs is reasonable when studies evaluated 100 SNPs from candidate genes. But now that GWAS* (genome-wide association studies) *assays include 1 million SNPs or more*, *the number of combinations to test has exploded* …" (8), with all the expected consequences. Finally, correction for confounding factors and covariates is still an unmet need, as it is the common lack of replication and validation datasets to confirm the results of a previous study.

Going back to the RCC field, the above complexity, ultimately hampering our ability to draw conclusions from SNPs studies which could be useful in everyday clinical practice, is well evidenced by a recent paper investigating a model which integrates pharmacokinetics, pharmacodynamics, pharmacogenetics, and clinical outcome in patients with mRCC (and metastatic colo-rectal cancer) treated with sunitinib (10). Given the above premises, it is not strange—but still remains frustrating—that in mRCC patients only baseline soluble vascular endothelial growth factor receptor (VEGFR)-2 levels (and no other, more sophisticated, parameters) proved to be associated with clinical outcome (10).

As a whole, what is quite clear, in our opinion, is that SNPs have only few of the characteristics of the so-called "ideal" biomarker, as reported in *Table 1* (11,12), and definitely not the most important ones.

Table 1 Characteristics of an "ideal" biomarker [modified from references (11,12)]

Routinely accessible
Rapidly available (short turn-around time)
Easily quantifiable
Cost-effective
Reproducible
Accurate
Endowed by good sensitivity and specificity
High predictive values
Good correlation with the outcome of interest
Predictor of a key ("hard") endpoint—ideally, OS
Easy to interpret
Objective
Stable (i.e., kinetic independent of internal or external conditions)
Non (or at least minimally) invasive

How does it fit into the landscape of the presently highly mentioned personalized/precision medicine?

Well, it is our (of course debatable) opinion that although a precision Medicine approach represents for sure the near future—also in the field of Oncology, we still need to undoubtedly demonstrate that a personalized/precision medicine approach could lead to a substantial improvement in some really relevant outcomes (13). This is also the case for SNPs research in RCC.

Should we thus desist to persist to use SNPs?

Probably not, but we do badly need to change the way we conduct this kind of researches; we do not longer need small, single-centre studies; a coordinated international effort is warranted in order to standardize methodology (as well as statistical analysis), design adequately powered studies (possibly prospective), analyze resulting data, replicate and validate them, and finally design clinical trials aimed at demonstrating the possibility of improving certain outcomes (of efficacy and/or of tolerability) basing on the use of these biomarkers.

What will remain of these researches in the future, is presently not known: either just some publications retrievable on the PubMed site, or a prognostic/predictive tool really able to change everyday management of RCC patients. Presently, the first option seems more likely …

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Nebert DW, Vesell ES. Chapter 19 - Pharmacogenetics and Pharmacogenomics. In: Rimoin DL, Pyeritz RE, Korf BR. editors. Emery and Rimoin's Principles and Practice of Medical Genetics (Sixth Edition). Cambridge, MA: Academic Press, 2013;19:1-27.
2. George DJ, Martini JF, Staehler M, et al. Phase III Trial of Adjuvant Sunitinib in Patients with High-Risk Renal Cell Carcinoma: Exploratory Pharmacogenomic Analysis. Clin Cancer Res 2019;25:1165-73.
3. Ravaud A, Motzer RJ, Pandha HS, et al. Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy. N Engl J Med 2016;375:2246-54.
4. Dornbusch J, Walter M, Gottschalk A, et al. Evaluation of polymorphisms in angiogenesis-related genes as predictive and prognostic markers for sunitinib-treated metastatic renal cell carcinoma patients. J Cancer Res Clin Oncol 2016;142:1171-82.
5. Beuselinck B, Zucman-Rossi J. Kidney cancer: single nucleotide polymorphisms in mRCC: is their time up? Nat Rev Urol 2015;12:424-6.
6. Diekstra MH, Swen JJ, Boven E, et al. CYP3A5 and ABCB1 polymorphisms as predictors for sunitinib outcome in metastatic renal cell carcinoma. Eur Urol 2015;68:621-9.
7. van der Veldt AA, Boven E, Helgason HH, et al. Predictive factors for severe toxicity of sunitinib in unselected patients with advanced renal cell cancer. Br J Cancer 2008;99:259-65.
8. Ritchie MD, Van Steen K. The search for gene-gene interactions in genome-wide association studies: challenges in abundance of methods, practical considerations, and biological interpretation. Ann Transl Med 2018;6:157.
9. Zhang S, Tan IB, Sapari NS, et al. Technical reproducibility of single-nucleotide and size-based

DNA biomarker assessment using DNA extracted from formalin-fixed, paraffin-embedded tissues. J Mol Diagn 2015;17:242-50.
10. Diekstra MH, Fritsch A, Kanefendt F, et al. Population Modeling Integrating Pharmacokinetics, Pharmacodynamics, Pharmacogenetics, and Clinical Outcome in Patients With Sunitinib-Treated Cancer. CPT Pharmacometrics Syst Pharmacol 2017;6:604-13.
11. Martín-Ventura JL, Blanco-Colio LM, Tuñón J, et al. Biomarkers in cardiovascular medicine. Rev Esp Cardiol 2009;62:677-88.
12. Nora D, Salluh J, Martin-Loeches I, Póvoa P. Biomarker-guided antibiotic therapy-strengths and limitations. Ann Transl Med 2017;5:208.
13. Tannock IF, Hickman JA. Limits to Precision Cancer Medicine. N Engl J Med 2017;376:96-7.

Cite this article as: Porta C, Cosmai L, Rizzo M, Melazzini M. Single nucleotide polymorphisms in angiogenesis-related genes and outcomes from antiangiogenic therapies in renal cell carcinoma: really a step towards personalized oncology, or not at all? Ann Transl Med 2019;7(Suppl 1):S15. doi: 10.21037/atm.2019.01.51

