Molecular Markers to Predict Response to Therapy

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Currently approved treatments for metastatic renal cell carcinoma (RCC) include vascular endothelial growth factor (VEGF)-blocking agents, mammalian target of rapamycin (mTOR) inhibitors, and cytokine therapy. In the near future, we are likely to add immune checkpoint blocking agents to this list. As we develop treatment platforms around each therapeutic class, determining which drug is best for a particular patient becomes increasingly important. At this point, we do not have validated predictive biomarkers for patients with RCC. Here, we discuss the logistical challenges surrounding biomarker development, summarize the current crop of biomarker candidates, and explore potential avenues for the development of more effective predictive tools for patients with advanced RCC.
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There are currently eight US Food and Drug Administration–approved agents available for the treatment of metastatic renal cell carcinoma (RCC). Five of these agents target either vascular endothelial growth factor (VEGF) or its receptors (VEGFR), two inhibit activity of the mammalian target of rapamycin (mTOR)-related complexes, and one is a recombinant form of an endogenous cytokine, interleukin-2 (IL-2). Each of these agents provides clinical benefit to a subset of patients, and the overall outlook for patients with metastatic RCC is better than it was 10 years ago.

As outlined by Danila et al,[1] the specific contexts of use in which qualified biomarkers would influence medical decisions include the following:

1. *Detection*, use of the biomarker to establish a diagnosis;
2. *Prognosis*, measuring the probability of a specific clinical outcome, such as recurrence, progression, or survival;
3. *Prediction*, identifying the chance of response to a specific therapy;
4. *Response-indicator* biomarkers show a pharmacologic or physiologic response from the treatment (eg, a decline in prostate-specific antigen [PSA]), which does not necessarily mean that the patient has benefitted from a treatment;
5. *Efficacy-response* biomarkers are surrogates of how a patient feels or functions or how long he survives, extrapolating the clinical benefit;
6. *Treatment resistance* biomarkers define biologic determinants of failure or progression, such as second site mutations.

Each of these agent classes has a defined mechanism of action, and it stands to reason that a candidate-based approach to biomarker identification, credentialing, and validation should produce a set of prediction markers, and an iterative series of testing could generate response-indicator markers or efficacy-response markers. Unfortunately, despite efforts by numerous groups, we still lack a single prospectively validated marker or tool that can reliably predict clinical benefit in RCC. Reasons for this failure include the absence of strong candidates or the interaction of multiple factors, inadequate sample size of the studies undertaken to perform biomarker identification, and the absence of follow-up validation studies for the few candidates currently being proposed.

Additionally, the mechanics, logistics, and legal aspects surrounding tissue collection and processing itself can produce challenges for the investigator interested in developing a biomarker. Genomic tumor heterogeneity adds to the challenge.

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This review addresses the logistical challenges of tissue and data handling required for biomarker development, and then moves into the description of major categories of candidates being evaluated in RCC.

CHALLENGES WITH TISSUE AND DATA COLLECTION

Two different types of collections must occur to really identify a predictive biomarker in renal cancer: tissue collection and data collection.

Tissue Collection

Tissue collection is the critical issue and major limitation for any translational project. Though many attempts have been made to systematically guarantee biologic material is stored properly for research, major challenges remain 5 years later.[2] Major obstacles, and some proposed solutions, are listed here.

Legal and Ethical Challenges

Our increasing capacity for analyzing and using biologic samples has raised the question of where the limit should be placed separating what we can do from what we should do. The lack of clear references and limits in a field under constant evolution leaves researchers charged to discover what is technically possible, and to review boards to determine what is ethically permissible and patients to decide what is ultimately acceptable.

Currently, the way informed consent is requested and given replicates the way patient autonomy is preserved when deciding about a diagnostic or therapeutic procedure. Thus information about how samples will be obtained and stored is provided to patients before they are collected. In addition, an explanation about the biologic parameters that will be analyzed and foreseen consequences is also given. However, sometimes new techniques become available that did not exist when the consent was given, preliminary analysis within a project points to a new hypothesis that will require a different approach not described in the consent, and unexpected implications can potentially come from the results, affecting not only the patients but also their relatives, as in familiar syndromes.

In order to avoid ethical conflicts in translational research, some general advice can be given. First, informed consent must be carefully designed to specifically ask for permission for further studies beyond the scope of the initial project. Second, patients must be aware of the possibility of unexpected findings and be asked about their willingness to receive information in such cases. Finally, anonymity procedures, whenever possible, are strongly encouraged as the easiest way to reconcile patient privacy and future uses of samples.

Technical Aspects

There are several circumstances regarding tissue acquisition, processing, and analysis that can affect the results of a study and, at least partially, explain contradictory conclusions between different projects.

Perioperative variables, such as type and duration of anesthesia, blood pressure variations, or the surgical procedure itself can impact biological markers like the phosphorylation status of the cellular pathway.[3] These parameters cannot be controlled, but some investigators are trying to develop systematic procedures to record them properly.[2]

Postsurgical tissue handling conditions are important, especially for the assessment of RNA. Tissue should not be kept at room temperature and preservation in ice or cryopreservation media is encouraged.

In addition, fixation-related parameters are important. For example, type of fixative can be responsible for mutation artifacts, and fixation time influences tissue antigenity.[4] Standardization of such processes according to international guidelines is key.

Finally, it must be taken into account that every technique has its own limitations and biases. Thus, replication of any results by independent groups is nowadays considered essential to ensure the reliability of any conclusion.

Clinical Data Collection

Collecting reliable clinical data is a key point in translational research, and can be even more challenging than obtaining adequate biological samples. Medical records are not always available for review and, even so, getting accurate information is time-consuming. Data regarding some variables can be poorly recorded in daily practice or simply absent if they were considered to be irrelevant by the attending physician. Thus, prospective studies, where the key data points are defined before trial initiation, are clearly preferred over retrospective evaluations. External monitoring also would be ideal, although most of the time it is not feasible due to the high cost.

Tumor Heterogeneity

Practical considerations dictate that tumor tissue analysis is performed on relatively small tumor samples. The constraints faced by the physician include the amount and number of samples acquired in the case of biopsies, with multiple or larger biopsy samples being impractical from a safety standpoint, and the time and effort required to assess multiple independent samples if larger