Drug Resistance Updates 17 (2014) 77–88

Contents lists available at ScienceDirect

Drug Resistance Updates

journal homepage: www.elsevier.com/locate/drup

Review

Predictive biomarkers in renal cell cancer: Insights in drug resistance mechanisms

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ARTICLE INFO

Keywords:
Renal cell carcinoma
VEGF targeted therapy
Predictive biomarker

ABSTRACT

Introduction: VEGF-targeted therapy is currently the first line treatment for patients with metastatic clear cell renal cell carcinoma (ccRCC), but most patients either display primary (intrinsic) resistance or acquire drug resistance. In recent years multiple mechanisms of resistance to VEGF-targeted therapy emerged from preclinical research, but it is currently unknown to what extent these drug resistance modalities play a role in the clinic. Here we reviewed the current literature on biomarkers that predict treatment outcome in patients with ccRCC to gain insight in clinical drug resistance mechanisms.
Methods: A search syntax was compiled by combining different synonyms of "biomarker" AND "renal" AND "cancer". MEDLINE was accessed through PubMed, where this syntax was entered and used to search titles and abstracts of publications. Articles were selected based on three criteria: (1) description of patients with clear cell RCC, (2) treatment with VEGF targeted therapy and (3) discussion of biomarkers that were studied for potential association with treatment response.
Results: The literature search was performed on March 4th 2014 and yielded 1882 articles. After carefully reading the titles and abstracts based on the three previously mentioned criteria, 103 publications were evaluated. Backward citation screening was performed on all eligible studies and revealed another 24 articles. This search revealed that (1) High glucose uptake and low contrast enhancement on PET- and CT-imaging before start of treatment may correlate with poor response to therapy, (2) Low dose intensity due to treatment intolerance is related to shorter progression free survival. (3) Acquired resistance appears to be associated with rebound vascularization based on both longitudinal monitoring of contrast enhancement by CT and blood vessel counts in tumor tissue, and (4) Based on plasma cytokine and single nucleotide polymorphism (SNP) studies, interleukin-8, VEGFR-3, FGFR2 and HGF/MET emerged as potential clinical markers for chemoresistance.
Conclusion: Low dose intensity, specific tumor-imaging techniques and potential biological biomarkers may be predictive for response to VEGF-targeted therapy in ccRCC. Some of these plausible biomarkers may also provide more insight into the underlying mechanisms of resistance such as altered glucose metabolism and rapid rebound vascularization.

Contents

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http://dx.doi.org/10.1016/j.drup.2014.10.003
1368-7646/

1. Background

Recent molecular characterizations of renal cell carcinoma by the cancer genome atlas (TCGA) and others provide a comprehensive view on the altered pathways and cellular processes (Cancer Genome Atlas Research Network, 2013). The vast majority (80%) of clear cell renal cell carcinoma (ccRCC) harbors inactive pVHL, resulting in the accumulation of hypoxia inducible factors (HIFs). Increased activity of these transcription factors appears to be responsible for the rich vascularization as well as the tendency to metastasize (Vanharanta et al., 2013). The HIF inducible gene VEGF is a crucial player in angiogenesis and has been recognized as an important therapeutic target for patients with ccRCC. Drugs targeting VEGF have significantly improved overall survival and represent a milestone in the treatment of metastatic ccRCC. Currently five VEGF directed drugs (pazopanib, sunitinib, axitinib, sorafenib and bevacizumab) are FDA approved with sunitinib and pazopanib as preferred first line agents (Motzer et al., 2007; Sternberg et al., 2010). Initially, most patients have clinical benefit as shown by disease stabilization or regression according to RECIST. However, in approximately 25% of the patients with metastatic RCC, intrinsic resistance to treatment is observed during first line VEGF targeted therapy (Heng et al., 2012). Despite incidental reports on durable responses, most other patients eventually develop drug resistance.

In general two modes of resistance to angiogenesis inhibitors have been recognized in preclinical studies, being intrinsic (pre-existing) non-responsiveness and acquired (evasive) resistance (Bergers and Hanahan, 2008). Acquired resistance may be mediated by the upregulation of alternative angiogenic factors (FGFs, ephrins and angiopoietins), recruitment of bone marrow derived cells or increased pericyte coverage (Casanovas et al., 2005; Yang et al., 2004; Mancuso et al., 2006). In addition to angiogenesis related effects, resistance can also be caused by effects on tumor cells, for example by adaptation of cancer cells toward a more invasive phenotype (Paez-Ribes et al., 2009). Particularly from tyrosine kinase inhibitors (TKIs) it is known that they also inhibit proliferation of tumor cells directly. We previously found that sunitinib sequestration in lysosomes of tumor cells may interfere with the antitumor effects and represent an alternative resistance mechanism (Gotink et al., 2011). Consistently, previous studies have shown that hydrophobic weak base anticancer drugs dramatically sequester in lysosomes (Adar et al., 2012). Moreover, it was found that carcinoma cells harboring the multidrug resistance phenotype, harbor a markedly increased number of lysosomes per cell. Acquired mechanisms of drug resistance were suggested to be similarly involved in intrinsic drug resistance, however in this case as a pre-existing condition. Some additional factors were reported, such as inactivating mutations in TP53, that may allow tumor cells to grow under relative hypoxic conditions and therefore evade the effect of angiogenesis disruption (Yu et al., 2002). Although VEGF-targeted drugs do inhibit VEGF signaling, the majority of TKIs competitively bind to the ATP-binding pockets of a variety of other kinases that could also convey therapeutic effects (Gotink and Verheul, 2010). As a consequence, additional resistance mechanisms may exists that are unique for each drug, but these are currently unknown.

Which of the mechanisms described above, predominantly applies to patients with RCC is unclear. In order to select patients that may benefit from VEGF-targeted therapy, multiple studies have aimed to identify biomarkers predictive for response. Predictive biomarkers typically foretell which patient will respond to the treatment or will have no benefit. Together with recent literature on the genetic alterations and gene expression profiles in RCC, predictive biomarkers may also give insights in drug resistance mechanisms in patients and provide clues for rational combination strategies. We reviewed the recent literature on predictive biomarkers for VEGF-targeted therapy in patients with RCC to gain insight in clinical drug resistance mechanisms.

Table 1
Search syntax.

(biomarker[tiab] OR marker[tiab] OR (response[tiab] AND predict*[tiab])) AND (renal[tiab] OR kidney[tiab] OR RCC[tiab]) AND (cancer[tiab] OR carcinoma[tiab] OR tumor[tiab] OR tumour[tiab])

2. Methods

We performed a systematic search for publications archived in MEDLINE on predictive biomarkers in RCC. A search syntax was compiled by combining different synonyms of "biomarker" AND "renal" AND "cancer" (Table 1). MEDLINE was accessed through PubMed, where this syntax was entered and used to search titles and abstracts of publications. All English publications that appeared in MEDLINE after 1-1-2006 (FDA approval of the first targeted agent) were included in the search. Subsequently abstracts were carefully evaluated. Full text versions were obtained through Harvard University Library from articles describing clear cell renal cell carcinoma (ccRCC), treatment with VEGF targeted therapy (sunitinib, pazopanib, sorafenib, axitinib, and bevacizumab) and biomarkers that displayed association with treatment response. Studies that measured treatment response according to RECIST guidelines were included in the review. Preclinical studies were excluded from the analysis. Biomarkers that only showed correlation with overall survival were considered prognostic biomarkers and also excluded. The search was performed on March 3rd 2014 and yielded 1882 articles. After evaluating the titles and abstracts based on the three previously mentioned criteria, 103 publications remained which were the basis for the current review. Backward citation screening was performed on all eligible studies and revealed another 24 articles. Potential biomarkers were divided into different categories. Clinical parameters, treatment side effects and imaging strategies were found to be correlated with treatment response. Molecular analysis of DNA, RNA and proteins in tumor tissue, circulating cells and blood yielded multiple predictive biomarkers that are all separately reviewed below.

3. Results

3.1. Clinical parameters: prognostic versus predictive biomarkers

Prognostic biomarkers that allow stratification of patients in different survival groups have been a long standing research topic in RCC studies. To this end multiple nomograms such as MSKCC, Cleveland Clinical Foundation (CCF) model and International Kidney Cancer Work Group (IKCWG) model were developed that