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Biologic tools to personalize treatment in genitourinary cancers☆

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Abstract

Background: Genitourinary (GU) cancers are a major healthcare issue in modern oncology. In the last decade many efforts have been made to develop new treatment options but with the possible exception of renal cell carcinoma, very few steps ahead have been taken. At the same time, a wide variety of molecular markers, potentially helpful in identifying patient subpopulation most likely to benefit from a specific treatment have been identified. Our goal is to clarify if biomarkers could be used at present to personalize treatment for GU cancers.
Materials and methods: Literature was search using PubMed and EMBASE using different terms and combinations regarding possible prognostic and predictive markers in renal, prostate and urothelial cancers.
Results: 3546 articles were retrieved. After excluding duplications, preclinical studies and factors without possible predictive value 654 publications remain. N-telopeptide, HER2/neu, EGFR, and p53 in prostate cancer, sVEGF-A for RCC and EMMPRIN and Survivin in urothelial cancer were among those identified. After a careful examination of published data, none of them reached a sufficient evidence to be suggested for use outside of clinical trials.
Conclusions: To date any reliable biomarkers has been validated for tailored treatments approaches in GU cancer. Future studies focusing on this issue are urgently needed.

Keywords: Prostate cancer; Urothelial cancer; Renal cell carcinoma; Predictive factors; Prognostic factors

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1. General information

Genitourinary (GU) cancers, namely prostate, urothelial and renal cell carcinomas, are a major healthcare problem in developed countries [1].

Available treatment options include surgery, chemotherapy, radiotherapy, hormone-therapy and, mainly for renal cell carcinoma (RCC), new biological agents. Despite a significant number of prognostic factors and models developed in the last years to identify different subsets of patients efforts to identify molecular markers able to predict treatment efficacy have been disappointing [2,3].

A predictive biomarker is defined as a "*characteristic*" that is objectively measurable as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a specified therapeutic intervention. Predictive biomarkers could ameliorate the cost/benefit ratio by increasing the efficacy in defined cohort of patients and reducing the number of not useful treatments and costs [4].

The ideal model of biomarker is HER2/neu. Overexpression of HER2/neu in breast cancer together with the availability of the molecularly targeted agents trastuzumab and lapatinib (this latter a tyrosine kinase inhibitor or TKI), has rendered possible a selective inhibition of this molecule with relevant clinical results in terms of progression free survival (PFS) and overall survival (OS) [5].

The presence of an highly expressed HER2/neu strongly predict for a benefit from the aforementioned targeted therapies, allowing personalized treatments based on molecular profile. Other examples of biomarkers routinely used for individualized treatments are c-kit expression in gatrointestinal stromal tumors (GIST) and estrogen/progesteron receptor (ER/PgR) status in invasive breast cancer [6–8].

Aim of this review is to define the state-of-the-art of predictive molecular biomarkers in the treatment of GU cancers.

2. Materials and methods

A through systematic search of the literature has been performed using PubMed and EMBASE and the acts of the principal international Oncological Meetings such as ASCO and ESMO. Selected potentially relevant publications for prognostic or predictive value were then assessed by two of us as independent reviewers, checking for the relevance of data provided about the suggested biomarkers. Controversies were solved by a third author.

3. Results

After exclusion of duplications and papers not involving clinical data, we identified 654 of 3546 potentially relevant reports, mainly addressing biomarker as a prognostic, and not predictive, factors.

3.1. Prostate cancer

Few potentially predictive biomarkers were retrieved (Table 1). Among them serum HER2/neu extracellular domain, p53 status and urinary N-telopeptide of type I collagen (uNTX) values [9–11]. Considering the high incidence of bone metastases and the availability of bone-targeting drugs such as bisphosphonates, markers of bone rearrangement looks particularly appealing as potential predictors of efficacy. In a recent report on 94 patients with castration-resistant prostate cancer, Rajpar et al. found that high uNTX levels significantly relate with overall survival, independently from other known prognostic factors (HR = 2.2; 95% CI 1.2–4.0). Of note uNTX, because produced as a consequence of proteases-induced collagen degradation in the bone, is considered a biomarker of bone rearrangement. All patients evaluated in the study were treated with the bisphosphonate zoledronic acid for at least two months, leading to the hypothesis that high uNTX values could identify a subpopulation with advanced bone disease who could benefit from such treatment [9].

HER2/neu is another potential predictive factor in prostate cancer. This molecule, a member of the EGFR family (together with EGFR 1, 3 and 4) plays a critical role in cancer cell survival and proliferation. Its prognostic and predictive value, clearly established in breast cancer , is emerging also for other cancer types such as gastric cancer [10]. The value of the HER2/neu soluble extracellular domain was investigated in a report by Domingo-Domenech et al. The authors reported a strong independent correlation among HER2 levels and both clinical response to docetaxel and survival [11]. Interestingly, these results could reply the ideal model of HER2 in breast cancer, where HER2 overexpression has been related with sensitivity to specific drugs such as antracyclines [12].

P53 is a nuclear protein critical for the regulation of apoptosis. Alterations in its functions, like inactivating mutations are notoriously related to chemotherapy and radiotherapy resistance. In the case of prostate cancer they are tought to confer resistance also to androgen deprivation. Che et al. analyzed in the large size study Radiation Therapy Oncology Group (RTOG) 9202, the value of p53 mutations in 777 patients with locally advanced prostate cancer treated with a combination of external beam radiation therapy (EBRT) and short-term or long-term androgen deprivation therapy (ADT). The authors found an inactivating p53 mutation in 168 of 777 treated cases (21.6%) and a statistically significant association with cause specific mortality (adjusted HR = 1.89; 95% CI 1.14–3.14; $p = 0.014$) and time to distant metastasis (adjusted HR = 1.72; 95% CI 1.13–2.62; $p = 0.013$). A significant association between assigned treatment and cause-specific mortality was shown in the subgroup with abnormal p53 by dividing patients into subgroups accordingly to p53 status only (adjusted HR = 3.81; 95% CI 1.40–10.37; $p = 0.0087$). When patients were divided into subgroups according to assigned treatment, only patients