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Review – Bladder Cancer

Inflammatory Biomarkers and Bladder Cancer Prognosis: A Systematic Review

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Abstract

Context: Host immune response has an impact on tumour development and progression. There is interest in the use of inflammatory biomarkers (InfBMs) in cancer care. Although several studies assessing the potential prognostic value of InfBMs in cancer have been published in the past decades, they have had no impact on the management of patients with urothelial bladder carcinoma (UBC).
Objective: To review and summarise the scientific literature on the prognostic value of tumour, serum, urine, and germline DNA InfBMs on UBC.
Evidence acquisition: A systematic review of the literature was performed searching the Medline and Embase databases for original articles published between January 1975 and November 2013. The main inclusion criterion was the provision of a survival analysis (Kaplan-Meier and/or Cox) according to the Reporting Recommendations for Tumor Marker Prognostic Studies guidelines for the assessment of prognostic markers. We focused on markers assessed at least twice in the literature. Findings are reported following Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines.
Evidence synthesis: Overall, 34 publications, mostly retrospective, fulfilled the main inclusion criterion. Main limitations of these studies were missing relevant information about design or analysis and heterogeneous methodology used. Inflammatory cells, costimulatory molecules in tumour cells, and serum cytokines showed prognostic significance, mainly in univariable analyses. High C-reactive protein values were consistently reported as an independent prognostic factor for mortality in invasive UBC.
Conclusions: There is a dearth of studies on InfBMs in UBC compared with other tumour types. Evidence suggests that InfBMs may have an impact on the management of patients with UBC. Currently, methodological drawbacks of the studies limit the translational potential of results.
Patient summary: In this review, we analysed studies evaluating the impact of inflammatory response on bladder cancer progression. Despite methodological limitations, some inflammatory biomarkers should be further analysed because they hold promise to improve patient care.

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1. Introduction

Evading the immune system is one of the emerging hallmarks of cancer [1]. It is well established that the inflammatory microenvironment has an impact on tumour prognosis, either positively or negatively [2]. The proper assessment of the composition and function of the microenvironment is challenging, and consensus is needed in the field about how to best consider the inflammatory response as a component of tumour subclassification [3]. In this regard, melanoma, colon, and breast cancer have taken the lead [4–6].

The definition of inflammatory biomarkers (InfBMs) is in itself challenging. Any molecule involved in innate or adaptive immune response could be considered; this makes the list of candidates very long, and it is difficult to establish a definition of InfBMs due to the interaction between inflammatory pathways and other cellular functions. In this review, we focus on markers with the primary known function in the immune response.

Urothelial bladder carcinoma (UBC) is highly prevalent. It represents an important economic burden, affects patient quality of life, and is life threatening when it invades muscle. However, in many ways, UBC remains a neglected disease [7]. The dearth of information on InfBMs and UBC is paradoxical, considering that UBC is one of the few tumours for which there is long-standing evidence of the efficacy of immunotherapy.

Studies on the prognostic value of InfBMs in UBC have been published since the 1970s [8–10]. The infiltration of the tumour by inflammatory cells and their association with prognosis has been explored more extensively than blood or urine cytokine levels and germline DNA polymorphisms in inflammatory genes. Unfortunately, none of these markers has proven to be sufficiently useful for clinical application. Methodological flaws, technical heterogeneity, and lack of appropriately designed validation studies have been the most important limitations. Guidelines were published in 2005 to improve the reporting of prognostic markers, but unfortunately they are rarely followed [11]. We report a systematic review of the published results and methods applied in studies that assessed tumour, blood, urine, and germline DNA InfBMs related to the prognosis of patients with UBC. The review was conducted following the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) guidelines criteria. The ultimate goals of this effort were to provide a rationale for promoting research in the promising field of immunity and UBC, to identify the main limitations of the studies performed, and to select the most promising markers for prospective studies and clinical trials through an integrative scope (Fig. 1).

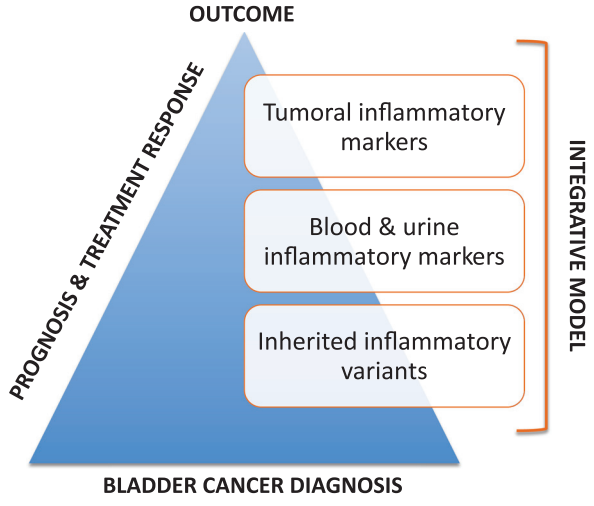

Fig. 1 – Integrative scope of inflammatory biomarkers to support urothelial bladder cancer patient prognostication and treatment response prediction.

2. Evidence acquisition

2.1. Material and methods

2.1.1. Information sources and eligibility criteria

The Medline, Medline In-Process, and Embase databases were searched for all original articles published from January 1975 to November 2013 on the topic of interest. Medline was searched through PubMed. Reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines.

The inclusion criteria were (1) original article, (2) human research, (3) English language, (4) accessibility to the full manuscript, and (5) availability of Kaplan-Meier/Cox regression-derived results about the prognostic value of the InfBMs on UBC outcomes according to the REMARKS guidelines for assessment of a prognostic marker [12]. Studies using association tests instead of survival analysis, with or without adjustment for other relevant variables, were not included, but they are listed in Supplementary Table 1. The outcomes considered were recurrence and progression for non–muscle-invasive bladder cancer (NMIBC) and local progression, metastasis, and cancer-specific mortality and overall mortality for NMIBC and muscle-invasive bladder cancer (MIBC). We report on studies assessing an InfBM twice or more in the literature. All other studies are listed in Supplementary Table 1.

2.1.2. Search strategy

We searched PubMed using the controlled vocabulary of the Medical Subject Heading database along with open text. The algorithm applied was (bladder OR urothelium OR transitional cell) AND (cancer OR tumour OR tumour OR carcinoma OR neoplasm) AND (inflammation OR inflammatory OR immune OR immunity) AND (prognosis OR survival OR recurrence OR progression). The search in Embase used the Emtree vocabulary ‘bladder cancer’ AND (‘inflammation’ OR ‘immunity’) AND ‘prognosis’. All selected articles were further hand-searched to identify additional relevant articles.

2.1.3. Study selection and the data collection process

The first stage of the search in Medline and Embase was performed by A.M.L. to screen and exclude studies unrelated to UBC or InfBMs. Second-stage selection was performed by four investigators (A.M.L., Y.A., F.X.R., and N.M.).