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Urologic Oncology: Seminars and Original Investigations ▮ (2018) ▮▮▮–▮▮▮

UROLOGIC ONCOLOGY

Review article

Circulating tumor cells in bladder cancer: Emerging technologies and clinical implications foreseeing precision oncology

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Received 22 November 2017; received in revised form 31 January 2018; accepted 12 February 2018

Abstract

Context: Circulating tumor cells (CTC) in peripheral blood of cancer patients provide an opportunity for real-time liquid biopsies capable of aiding early intervention, therapeutic decision, response to therapy, and prognostication. Nevertheless, the rare and potentially heterogeneous molecular nature of CTC has delayed the standardization of robust high-throughput capture/enrichment and characterization technologies.

Objective: This review aims to systematize emerging solutions for CTC analysis in bladder cancer (BC), their opportunities and limitations, while providing key insights on specific technologic aspects that may ultimately guide molecular studies and clinical implementation.

Evidence acquisition: State-of-the-art screening for CTC technologies and clinical applications in BC was conducted in MEDLINE through PubMed.

Evidence synthesis: From 200 records identified by the search query, 25 original studies and 1 meta-analysis met the full criteria for selection. A significant myriad of CTC technological platforms, including immunoaffinity, biophysical, and direct CTC detection by molecular methods have been presented. Despite their preliminary nature and irrespective of the applied technology, most studies concluded that CTC counts in peripheral blood correlated with metastasis. Associations with advanced tumor stage and grade and worst prognosis have been suggested. However, the unspecific nature, low sensitivity, and the lack of standardization of current methods still constitutes a major drawback. Moreover, few comprehensive molecular studies have been conducted on these poorly known class of malignant cells.

Conclusion: The current rationale supports the importance of moving the CTC field beyond proof of concept studies toward molecular-based solutions capable of improving disease management. The road has been paved for identification of highly specific CTC biomarkers and novel targeted approaches, foreseeing successful clinical applications.

Keywords: Bladder cancer; Circulating tumor cells; Clinical implications; Liquid biopsies; Systematic review; Technologies

1. Introduction

Advanced bladder cancer (BC) presents significant management hurdles concerning its high recurrence rates,

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https://doi.org/10.1016/j.urolonc.2018.02.004
1078-1439/

rapid progression, poor response to chemotherapy, and lack of novel targeted therapeutics [1]. In addition, significant variations in therapeutic outcomes are observed for tumors of apparently similar histology, mostly due to their high molecular heterogeneity [2]. Prognostication difficulties are often aggravated by the absence of efficient follow-up strategies, especially of noninvasive nature, for real-time monitoring of therapy response, metastatic risk assessment, and early detection of occult micrometastases.

Circulating tumor Cells (CTC), derived from primary tumors by passive shedding or dynamic stromal invasion, are regarded responsible for disease dissemination [3]. Once in the bloodstream, CTC capable of overcoming sheer stress and evading the immune system may reach distant organs, whose microenvironment endows its expansion and differentiation or induces temporary quiescence [3] (Fig. 1). Despite being the driving force of metastasis, CTC account for less than 0.004% of all mononucleated blood cells [4]; nevertheless, recent data suggest that CTC counts may be explored to improve disease management. CTC were proven to better predict overall survival than other cancer-circulating biomarkers as free DNA [5], holding tremendous potential for aiding early intervention, therapeutic decision, and therapy response assessment [6]. Nevertheless, it is likely that both CTC and circulating tumor DNA (ctDNA) platforms may have complementary roles in prognosis and metastasis assessment [5]. CTC may also reflect the genetic drift between primary and metastatic tumors [7], paving the way for liquid biopsies in alternative to metastatic biopsies. Moreover, CTC may be selectively recovered from patient's blood, expanded in vitro, and xenografted into relevant animal models, enabling drug susceptibility evaluation, biomarker discovery, and personalization of targeted therapeutics toward true precision medicine settings [8,9]. However, the scarceness and potentially heterogeneous molecular nature of CTC requires high-throughput capture/enrichment, detection and characterization technologies, ideally at a single cell level, which has delayed the standardization of robust methods for CTC implementation in clinical practice [10]. Nevertheless, in the last decade, numerous platforms have been presented envisaging this end, namely, flow cytometry-based assays and lab-on-a-chip microfluidic devices [10,11] (Fig. 2). This review aims to systematize emerging solutions for CTC analysis in BC, as well as its opportunities and limitations, while providing key insights on specific technologic aspects that may ultimately guide clinical implementation.

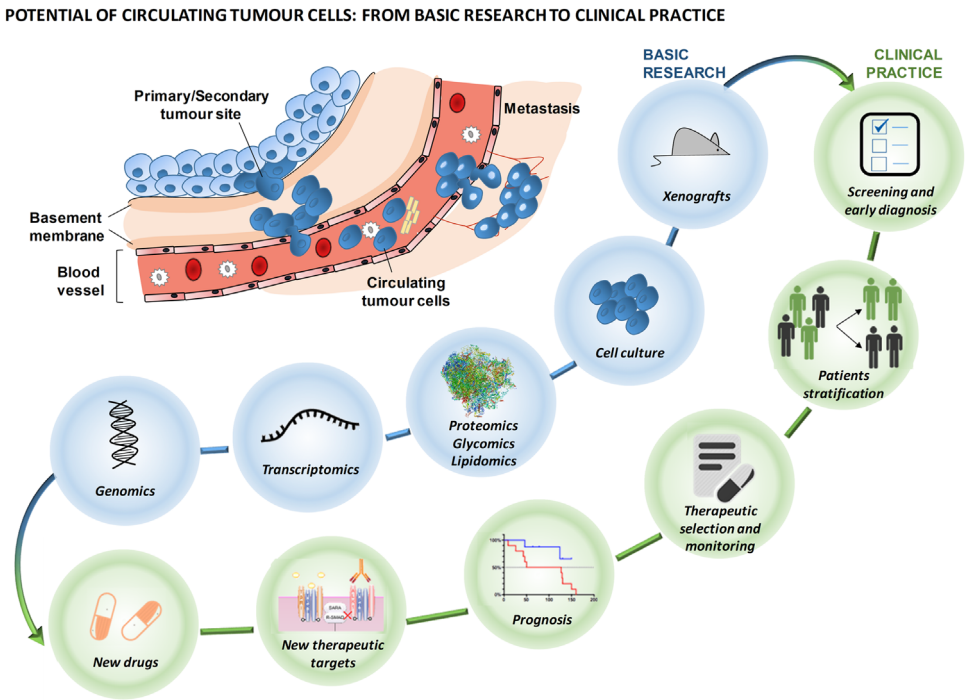

Fig. 1. Illustration of the involvement of circulating tumor cells (CTC) in the metastatic cascade and their potential in basic research and clinical practice. Once in the bloodstream, CTC capable of overcoming sheer stress and evading the immune system may extravasate to distant organs, whose microenvironment endows its expansion and differentiation or induces quiescence. The minimally invasive CTC isolation from patient's blood provides the opportunity for a "real-time liquid biopsy," allowing the assessment of genetic and proteomic differences between the primary and metastatic tumors, and the identification of drug-resistant phenotypes as well as CTC subpopulations with actionable molecular characteristics. Moreover, ex vivo model development (cell cultures, animal xenografts) could be a crucial milestone to aid therapeutic decisions and test novel drugs. As such, CTC molecular characterization through basic research can aid early diagnosis, monitoring of disease evolution, prediction of therapy response to targeted approaches, patient stratification, and eligibility for clinical trials, improving prognosis in everyday clinical practice. (Color version of figure is available online.)