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EDITORIAL

# Immunotherapy for bladder cancer: the fight is on

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Each year, cancer costs the health care systems of the 27 countries in the EU €51 billion [1]. Bladder cancer (BCa) is ranked the 11th most common cancer in the world, and over 50% of cases occur in developed countries. BCa is the sixth leading cause of cancer in the EU, with 124,000 people diagnosed and > 40,000 people dying from the disease each year. By 2030, the annual incidence is projected to increase to 219,000, two-fifths of this due to the ageing of the European population [1, 2]. For many years, BCa has been considered as a so-called "orphan disease" in the field of onco-urology compared to prostate cancer, notably because of limited funds invested for BCa research. In addition, there was no specific media coverage of the disease with articles containing a relevant "red-flag" symptom box helping in providing a better representation of public health strategies: screening and public information campaign. Treatment for patients with locally advanced and metastatic BCa remains unsatisfactory [3, 4]. Thus, general objectives in BCa are twofold: (1) increased quality of delivered health care and (2) better use of available treatments in therapeutic strategies.

For the patients who present non-muscle-invasive bladder cancer (NMIBC), more than 50% of them are likely to undergo a recurrence and a progression of the disease despite active endoscopic surgical treatment and adjuvant Bacillus Calmette–Guérin (BCG) intravesical instillations. The administration of BCG immunotherapy has become the standard of care for high-grade NMIBC and carcinoma in situ (CIS) in terms of prevention of recurrence and progression [3]. The data establishing BCG immunotherapy as the standard of care for high-grade NMIBC and CIS over other bladder instillation modalities are presented in addition to the effect maintenance that BCG therapy has on sustaining the immuno-protective effect. BCG was, indeed, the first immunotherapy, and it is currently the most effective treatment of NMIBC and one of the most successful applications of immunotherapy to the treatment of cancer [3, 5]. However, there is a worldwide BCG shortage (Connaught strain) and the reality is that there is a lack of robust alternative treatment in high-risk NMIBC [6, 7]. For the patients who present muscle-invasive bladder cancer (MIBC) without evidence of metastasis, the gold-standard treatment remains cystectomy with subsequent consequences on quality of life [8] combined with systemic chemotherapy [5]. Finally, for the patients who present de novo metastatic BCa (10–15%), and those in whom the disease recurs despite treatment with curative intent (50%), the prognosis is a dismal for 3–6 months [2, 5]. In an attempt to improve upon this poor outlook, cisplatin-containing combination chemotherapy has been the standard of care since the 1980s. Only modalities and schedule of Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (MVAC) chemotherapy administration have slightly evolved over time but roughly, nothing has changed for 40 years! The original MVAC studies founded the concept of cisplatin combination chemotherapy as they showed significant response improvements (39% vs. 12%; $p < 0.0001$) compared to single agent cisplatin, with PFS and OS rates of 10 months vs. 4.3 months and 12.5 months vs. 8.2 months, respectively [5, 9].

The use of immunotherapy was based on the following three observations: recognition of spontaneous regression, presence of a T-cell immune response, and tumour regressions associated with cytokine treatment [10]. Currently, the rapidly evolving field of immuno-oncology is yielding novel immunotherapeutic agents. Several novel immunotherapy agents, such as checkpoint inhibitors, programmed cell death-1 (PD-1 present on T cells), one of its ligands (PD-L1 present on antigen-presenting cells and tumour cells), and cytotoxic T-lymphocyte-associated protein-4 pathways or CTLA-4, are being studied in metastatic BCa and are showing promise as important steps in the management of this disease [10]. However, immunotherapy agents rarely cause durable tumour regressions and most patients will

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eventually experience disease progression in the metastatic setting. Checkpoint inhibitors are some of the strategies being considered also in locally advanced MIBC and even in NMIBC [10–12].

Although the mechanisms of carcinogenesis are thought to be similar throughout the urinary tract, recent epidemiological data and genetic studies suggest otherwise [13]. It is now obvious that strong differences exist regarding tumour location and behaviour between the upper and lower urinary tracts. Urothelial tumours can develop in a synchronous or metachronous multifocal manner at different urinary tract sites. The proposed schemes for the sequence of genetic events are neither exhaustive nor identical, but all agree that the tumour develops in several stages, each of which is associated with specific genetic changes. However, differences between the upper tract and lower tract urothelium have recently been described in the biological characteristics of the urothelium in the ureter and renal pelvis compared to the bladder [12, 14]. These results support the fact that UTUC and bladder UC have different tumourigenesis pathways. This trend demonstrates perfectly that new insights, new concepts, new clinical and basic research, and new therapeutic findings are becoming readily available. With all these new immunotherapy trials, we can expect a lot from ancillary fundamental basic research studies that will continue to focus on BCa [15, 16].

Management decisions in advanced BCa, including the appropriate use of pharmacological agents, are complex and attempts are being made to integrate evidence synthesis into clinical practice guidelines to improve problematic evidence-based decision-making [9]. Knowledge and incorporation of the existing evidence base for each therapy form a key component of this model. Therefore, I was particularly honoured and extremely grateful to the editorial board of the *World Journal of Urology* when they offered me the opportunity to propose such an issue to its readership. It is, in my opinion, a reflection of the scientific involvement of the editorial board of the *World Journal of Urology* in BCa, and it underlines its willingness to look ahead to the future of this important disease. In this issue, we provide an overview of all aspects in the field of BCa and immunotherapy that are progressing as a result of work by the best teams in the western world. Currently, we are in a time of exponential drug development, innumerable registered trials, and a vast amount of expenditure on immunotherapy cancer treatment (e.g., lung, breast, and melanoma), and BCa is just a small part of it. We have to be mindful that there are vast sums of money invested in what seems like a production line of new molecular-based therapies, and we are beholden to consistently challenge objectively the benefit that we realistically can afford for our patients.

I hope that you will enjoy reading this issue as much as I enjoyed preparing it for you.

Sincerely yours,
Professor Morgan Rouprêt

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