Review Article

Immunotherapy in urothelial carcinoma: fade or future standard?

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Abstract: Immunotherapy of non-muscle-invasive bladder carcinoma by Bacillus-Calmette-Guérin (BCG) instillation is a well-established treatment option since decades. Despite this fact, the immunocellular basis was first studied in recent years. New aspects of immunotherapy, also for progressed bladder carcinoma, might follow promising research on immunological targets.

Keywords: Bladder; urothelial carcinoma; Bacillus-Calmette-Guérin (BCG); immunotherapy

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Introduction

Approximately 110,000 people per year are diagnosed with urothelial bladder carcinoma in Europe (1). It is one of the ten most frequent neoplasms and the most common tumor disease of the genitourinary tract affecting men and women (2). There is a slight regional preference for developing bladder cancer in western industrial countries, with the highest incidences with more than 20 per 100,000 inhabitants in Denmark, The Netherlands and Spain (1). Bladder cancer incidence in the US increased from seven to 11 per 100,000 inhabitants in the first years of the 21st century (3). In most Asian countries urothelial bladder cancer is rare, in multiethnic countries, e.g., New Zealand, for the European population, incidence of urothelial bladder cancer is 100% higher than in the Maori and Asiatic group (4). The most important characteristics of bladder carcinoma are their high rates of multifocality and the trend towards recurrence in up to 70% of papillary tumors, which represent about 75% of bladder carcinomas (5). These lesions are restricted to the mucosal layer and stage pTa, while early-invasive tumours (pT1) reach the submucosal layer and approximately 15% of bladder cancers invade the musculous bladder wall (6).

Today the neoplasm is more likely to exist in men than in women with a two to three fold higher incidence for men: main cause of this is the fact that men are more exposed to risk factors of urothelial carcinoma, e.g., tobacco smoking and exposition to substances in working life. Especially tobacco smoking is responsible for nearly half of all urothelial carcinomas, leading up to a six fold increased risk compared with a non-smoker (7). In the last decades the number of females affected by urothelial bladder cancer increased due to a higher rate of tobacco smokers among women. It could be elucidated that these patients show worse cancer-specific survival over all stages of disease due to a lower awareness of bladder cancer and a thinner bladder wall (8).

Treatment of bladder carcinoma depends on its stage. While non-muscle-invasive tumors are treated only by transurethral resection and different instillation therapies, e.g., mitomycin or Bacillus-Calmette-Guérin (BCG), patients with muscle-invasive bladder cancer will undergo radical cystectomy. The EAU guidelines also propose to consider a radical treatment in case of pT1 urothelial carcinoma of the bladder (9). While immunologic aspects play a distinct role in the treatment of non-muscle-invasive disease, as seen with BCG instillation therapy, to date

there is no immunological treatment of progressed bladder carcinoma.

Bacillus-Calmette-Guérin (BCG) instillations as established treatment in non-muscle-invasive urothelial bladder cancer

Almost 40 years ago intravesical immunotherapy of non-muscle-invasive bladder cancer with BCG was first described (10). BCG was developed by Calmette and Guérin as an attenuated Mycobacterium bovis for vaccination against Mycobacterium tuberculosis (11).

To date, the exact mechanism of action of BCG in treatment of bladder cancer is not fully understood (12). Instillation of BCG induces an infection of the urothelial layer of the bladder wall. This leads to an activation of the reticuloendothelial system by granulocytes, macrophages and T-helper (Th) cells (13). BCG is internalized and presented via antigen-presenting cells, which leads to a cytokine response mediated by different Th1 and Th2 dependent cytokines. A study in which IFNγ urine levels were measured showed the positive effect of induction and maintenance therapy with BCG (14). To detect a response in IFNγ levels at least 3 weekly instillations are necessary and the IFNγ urine levels increase further with maintenance therapy. The antitumor activity is mediated by macrophages, cytotoxic T lymphocytes, natural killer cells and neutrophils (12).

Intravesical immunotherapy with BCG is recommended by common guidelines as state-of-the-art treatment for patients with intermediate or high-risk non-muscle-invasive bladder cancer (14). There are meta-analyses underlining the efficacy and superiority of BCG versus intravesical chemotherapy. Malmström *et al*. could show in a meta-analysis which included 9 randomized clinical trials with overall 2,820 patients comparing BCG and MMC that maintenance therapy with BCG significantly reduced the risk of recurrence (15). Concerning progression, overall survival and cancer-specific survival, no statistical significant difference was observed (16). Combining TURB with BCG significantly reduces recurrence rate of non-muscle-invasive bladder cancer compared with TURB alone (17). There are three more meta-analyses that underline superiority of BCG therapy over intravesical chemotherapy, the combination of chemotherapy and immunotherapy or no instillation therapy for risk of tumor recurrence (18-20). Comparing BCG and intravesical chemotherapy using mitomycin C, a meta-analysis of Böhle and Bock revealed a statistical significant benefit for BCG maintenance therapy (21). Furthermore, the combination of BCG maintenance and TURB is superior to TURB alone concerning risk of progression (22).

To date various different regimens exist, ideally the treatment regimen should consist of an induction therapy consisting of weekly applications for 6 weeks followed by a maintenance therapy for one to three years (15).

There are few studies concerning efficacy of different BCG strains. A prospective randomized trial comparing the two most common strains Connaught and Tice revealed a statistical significant difference between the two strains for recurrence-free survival, with a benefit for Connaught over Tice (23).

Side effects of the intravesical treatment with BCG can be divided into local and systemic side effects. Overall, BCG therapy is well tolerated by the patients. Maintenance schedule does not lead to an increase of side effects (24). Primarily infectious side effects like cystitis, prostatitis, epididymo-orchitis, fever or sepsis occur, as well as hematuria or allergic reactions. Immunocompromised patients are at higher risk to develop a systemic infection or systemic tuberculosis (15). To reduce side effects dose reduction has been discussed. Reducing the dose to one third does not reduce efficacy in intermediate risk tumors but is associated with a higher recurrence rate in high-risk tumors with no difference in toxicity (15).

Impact of leucocyte infiltration on prognosis of urothelial bladder cancer

While BCG therapy is ongoing for nearly forty years its action principle was unclear and even not studied for decades. New aspects of the impact of immune cell infiltration for cancer progression let start experimental studies on this topic. In 2006, Galon *et al*. for the first time showed the impact of leucocytes infiltrating tumor tissue in colorectal cancer. Low density of CD3 cells within tumor tissue was statistically highly significantly associated with worse cancer-specific survival (25). Further studies then led to the recommendation that leucocyte infiltration of colorectal tumours should be taken into account routinely in histopathological assessment (26). Despite the established clinical practice of using the proinflammatory effect of BCG instillations in adjuvant treatment of intermediate and high-risk non-muscle-invasive bladder cancer, the prognostic role of leucocyte infiltration in urothelial bladder carcinoma has not been studied for a long time.

Winerdal *et al*. made a start in 2011 showing a prognostic impact of CD3 cell infiltration in urothelial bladder carcinoma in 37 cystectomy specimens (27). In 2012 a work by Otto *et al*. followed, analysing the prognostic impact of T cell infiltration in early-invasive bladder cancer, probably the most challenging sub-entity of urothelial carcinoma with hardly foreseeable clinical courses (28,29). Data of Winerdal *et al*. in this study could be verified in 60 patients with stage pT1 bladder cancer that showed better cancer-sepcific survival in case of high density of CD3 cells in the tumour (28). In the same year, Biot *et al*. brought BCG therapy and leucocyte infiltration together in one analysis for the first time. They showed that after first BCG instillation interferon-γ-producing T cells were drained from lymph nodes and that in this case BCG therapy is successful (30). Nunez-Nateras *et al*. could show for treatment of stage pTis bladder cancer with BCG that infiltration of a special subset of Th cells (GATA3) is positive for the success of this therapy (31). In the same year 2014, Ceylan *et al*. could prove that at least for non-muscle-invasive bladder cancer a positive neutrophile-lymphocyte-ratio is associated with poor prognosis (32). Concerning muscle-invasive bladder cancer Sjödahl *et al*. could show the same result respecting low levels of CD3 in comparison to CD68 positive cells infiltrating the tumor (33). The fact that no further study on immunocellular infiltration has been published since 2014 reflects its neglected status.

New aspects of targeted immunotherapy for urothelial bladder cancer

The T-cell mediated immune response underlies several control mechanisms. To establish a targeted T-cell reaction activating as well as deactivating signaling pathways is necessary for self-tolerance maintenance, minimization of damage to healthy cells and modulation of the strength and duration of normal physiological immune responses (34). Immune checkpoints are inhibiting pathways to control these T-cell functions and prevent the above mentioned auto-aggression. They consist of a ligand, expressed by the target cell, and a receptor, expressed by the effector cell—the T-cell. The ligand-receptor-complex leads to a deactivation of the T-cell response. Cancer cells harness this deactivation and thus manage to escape the anticancer immunity by overexpression of these specific ligands. Blocking the receptor-ligand-interaction using specific antibodies is a novel therapeutic anti-cancer approach which is being investigated on in several tumor entities (35). For example, nivolumab—a PD-1-inhibitor—has reached admission in second line therapy of metastatic renal cell carcinoma (36).

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) is expressed exclusively by activated CD8 T-cells and it executes its function via downregulation of Th cell activity and enhancement of regulatory T-cell (Treg) immunosuppressive mechanisms (37,38). Using monoclonal antibodies to block the CTLA-4 receptor leads to an activation of immune response depending on TH-cells. Clinical trials addressing the CTLA-4 inhibition are using ipilimumab as CTLA-4 antibody. First clinical benefits were reported in metastatic melanoma (39,40). Wang *et al*. recently showed a significant correlation between CTLA-4-polymorphisms and risk of bladder cancer in a case-control-study (41). By now there is one phase 2 trial that has investigated the effect of ipilimumab as neoadjuvant therapy in patients with muscle-invasive bladder cancer (42). Overall, 12 patients were included with six patients receiving two cycles of ipilimumab 3 mg/kg and six receiving two cycles ipilimumab 10 mg/kg. The study showed a tolerable safety profile and immunologic effects (42). Further randomized clinical trials are necessary to evaluate the efficacy of this drug in urothelial carcinoma of the bladder.

Programmed death 1 (PD-1) is expressed by activated T-cells and is one of the key checkpoint receptors (35). The ligands PD-L1 (B7-H1) and PD-L2 (B7-DC) are mainly expressed by tumor cells and stromal cells (43-45). Interaction of PD-1 and the immunosuppressive ligand PD-L1 (B7-H1) or PD-L2 (B7-DC) takes place in peripheral tissues and results in a suppression of T-cell activation and thus mediates immune resistance in the tumor microenvironment (46). There are several in vitro as well as clinical studies proving an enhanced antitumor immune activity by using antibodies against PD-1 and/or PD-L1 (36,47-49). Nakanishi *et al*. could show in 65 patients with urothelial carcinoma of the bladder, that tumors of higher grade and stage have a higher percentage of immunohistochemical expression of PD-L1 (50). They could also significantly correlate PD-L1 expression with recurrence and poor survival as well as independent prognostic factor in multivariate analysis (50). Using tissue microarray analysis in 302 patients with radical cystectomy, Xylinas *et al*. could demonstrate that PD-L1 expression predicts overall mortality after radical cystectomy (51). This was proven in another immunohistochemical analysis of 318 patients after radical cystectomy (52). Hereby, expression of PD-1 and PD-L1 was significantly associated with

advanced tumor stage and grade (52). Right now only few clinical trials using PD-1 or PD-L1 inhibitors in urothelial bladder cancer are on the way. Preliminary results of the KEYNOTE-012 trial were presented at the ASCO-GU 2015 by O'Donnell *et al.* (53). In this trial 33 patients with metastatic bladder carcinoma and with 2 prior systemic therapies were enrolled and received pembrolizumab (a PD-1 antibody) 10 mg/kg every 2 weeks. Only patients with expression of PD-L1 in tumor stroma or tumor cells were eligible. The drug showed an acceptable safety and tolerability profile with promising antitumor activity [response rate of 24% and seven partial responses (53)]. Anti-PD-L1 antibodies also seem to have an antitumor effect in metastatic bladder carcinoma. Kim *et al*. could show that MPDL3280A (a PD-L1 antibody) can induce rapid and durable responses especially in patients with high expression of PD-L1 in immunohistochemistry, while being well-tolerated (54). Further clinical studies are of course necessary to prove this effect and establish the anti-PD-1 and anti PD-L1 drugs as therapeutic options. What all the ongoing trials could show, is an improved efficacy in tumors with high PD-1 or PD-L1 expression, suggesting a patient tailored therapy.

Treatment related adverse events can be observed in 30–50% for all adverse events and in 6–14% for grade 3/4 adverse events (35). Side-effects are mostly caused by auto-immune mechanisms and resulting in dermatologic problems (i.e., dermatitis, rash and vitiligo), gastro-intestinal side-effects (i.e., colitis, hepatitis and mucositis), pneumonitis and thyroiditis (Topalian *et al.*). Most common adverse events are fatigue and nausea. The grade 3/4 adverse events can be seen more frequently in CTLA-4 inhibitors (34). A correlation between occurrence of side-effects and severity with the tumor response rate has been reported (55,56).

Conclusions

Despite being used since decades by urologic clinicians, inflammatory reactions in bladder cancer are less studied. Applied by BCG instillation therapy since the 1970s only in recent years impact of leucocyte infiltration on bladder cancer prognosis was studied. In first preliminary analysis it could be shown that high levels of immunocompetent cells in the tumor promote success of BCG treatment and is associated with better survival in non-muscle-invasive and muscle-invasive bladder cancer. Therapeutic consequences for muscle-invasive and metastatic disease might follow ongoing studies on new targets like PD1-antibodies. Taken together, immunotherapeutical aspects are a promising but underrepresented field of urological research.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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