Immuno-oncology in transitional cell carcinoma

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SUMMARY

Immunotherapy has been used in the treatment of localised, high-risk transitional cell carcinoma. Bacillus of Calmette-Guérin therapy is a standard treatment for patients with non-invasive transitional cell carcinoma with bad prognostic factors (high-grade pTa; carcinoma in situ) and early stage invasive bladder cancer (pT1) after transurethral resection of the bladder. Recently, based on phase II trials, atezolizumab, an inhibitor of PD-L1, and nivolumab, an inhibitor of PD1, have been registered for the treatment of patients with metastatic transitional cell carcinoma progressing after a platinum-based chemotherapy for metastatic disease. Pembrolizumab, a monoclonal antibody against programmed death receptor-1 was registered based on a phase III trial in this setting resulting in a survival benefit compared to second-line chemotherapy. Predictive markers are being explored for a better patient selection for the treatment of transitional cell carcinoma.

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INTRODUCTION

Immunotherapy has been used since the 1970s in the treatment of localised transitional cell carcinoma (TCC) of the urothelial system and has recently been introduced in the treatment of patients with metastatic disease. It is also being tested as adjuvant treatment in patients with urothelial tumours with bad prognostic characteristics.

This review discusses the role of the immune system in TCC, the clinical effects of immunotherapy in localised and metastatic TCC and the use of biomarkers to predict response to treatment.

THE IMMUNE SYSTEM IN TRANSITIONAL CELL CARCINOMA

The immune system is able to recognise antigens that are different from own body cells and are expressed by mutated cells. The mutational load in bladder cancer is ranking among the highest compared to other cancers, making it an ideal candidate for recognition by the immune system and immunotherapy.[1]

Two important immune events are taken place in the recognition and control of cancer cells.

Antigens that are released by cancer cells are taken up by antigen-presenting cells (APCs), modified and presented to the immune system, mainly to the cytotoxic T cells (initiation phase). The activated immune cells are transported to the tumour and, by recognition of specific antigens, are able to destroy tumour cells (effector phase).

Tumour cells are able to modify these responses by interfering with checkpoints at the immune cycle. They are able to modify the initiation phase by inhibiting the priming of T cells via the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) complex and the effector phase by interfering with the programmed cell death receptor (PDR) system

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Conflict of interest: D. Schrijvers participated in clinical trials with immunotherapy in bladder cancer.

Key words: bladder cancer, immune therapy, localised, metastatic.

TABLE 1. Effect of Bacillus of Calmette-Guérin on relapse of high-grade non-muscle-invasive transitional cell carcinoma.

Author	N° pts	Control arm	Experimental arm	Results
Malmström	2,820	MMC	BCG + BCG MT BCG- BCG MT	32% ↓ relapse BCG + BCG MT 28% ↑ relapse BCG - BCG MT
Houghton	801	BCG + MT	CT + BCG MT	No ↓ relapse with CT
Astram	2,719	FD BCG	LD BCG; VLD BCG	RR 0.86; better FD vs LD RR 0.66; better LD vs VLD

N°: number; pts: patients; MMC: mitomycin C; BCG: Bacillus Calmette-Guérin; MT: maintenance treatment; CT: chemotherapy; FD: full dose (81 mg); LD: low dose (27 mg); VLD: very low dose (13.5 mg); RR: relative risk; vs: versus.

(e.g., programmed death receptor ligand [PD-L]).[2]
Programmed death receptor ligand 1 (PD-L1) is expressed on TCC mainly in invasive and metastatic disease and is a prognostic factor in patients with TCC. It binds with the PDR and *B7-1*, present on cytotoxic T cells, and inhibits their activity.

LOCALISED TRANSITIONAL CELL CARCINOMA

In localised TCC, a local immune reaction is induced and this can be intensified by the use of Bacillus of Calmette-Guérin (BCG). The exact action mechanism of BCG is unknown, but it is causing a bladder infection at the level of normal and tumour tissue. BCG is taken up intracellularly and presents specific antigens with major histocompatibility class (MHC) 2 antigens on the infected cells, leading to an unspecific stimulation of the reticuloendothelial system causing a local inflammatory response with infiltration of granulocytes, macrophages and lymphocytes. The resulting inflammation causes release of a series of cytokines such as interleukins (IL)(IL-1, IL-2, IL-6, IL-8, IL-10, IL-12), tumour necrosis factor (TNF)-alfa, interferon (IFN) gamma, 'granulocyte/macrophage colony stimulating' factors and 'soluble intercellular adhesion molecule I'. The resulting immune response leads to tumour destruction.
In addition, BCG contains high levels of cytosine-phosphate-guanine oligodeoxynucleotide motifs that release TNF-related apoptosis inducing ligand (TRAIL) by the production of IFN. This results in apoptosis of cancer cells.[3]
In addition to a local response, tumour antigens released by apoptosis can be recognised by the immune system. Tumour antigens are taken up by APCs and are presented together with MHC2 antigens to T-lymphocytes. The activated T cells infiltrate the tumour and cause tumour cell destruction.[2] This system is regulated by different activating (e.g., OX40- OX40L, B7-1/CD86-CD28, CD137L-CD137) and immune suppressing interactions (e.g., CD80/DC86-CTLA-4, PD1-PDL1/PDL2, MCH2-LAG3).[4] Cancer cells can express factors that modify the immune system enabling cancer cells to avoid apoptosis.[4]
Local immune therapy with BGC is routinely used in patients with non-invasive TCC with bad prognostic factors (high-grade pTa; carcinoma in situ [CIS]) and early stage invasive bladder cancer [pT1]) after a transurethral resection of the bladder (TURB).[5]
Several meta-analyses have shown the positive effect in the prevention of recurrent TCC (*Table 1*):

- TURB in addition to adjuvant BCG is better than TURB alone or TURB and intravesical chemotherapy in preventing recurrence of non-muscle invasive high-risk TCC.[5]
- Intravesical BCG in combination with a maintenance treatment results in a decrease of local recurrence with 32% compared to intravesical chemotherapy with mitomycin C.[6]
- Addition of chemotherapy to a treatment with BCG does not give an additional benefit.[7]
- There seems to be a dose relationship of BCG in relation to a local recurrence.[8]

Based on these findings, the standard treatment with intravesical BCG is the administration of BCG (81 mg) weekly during six weeks followed by a maintenance BGC instillation of three-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months. In patients with intermediate-risk tumours, defined as tumours that are more extensive than a primary, solitary, TaG1 (Papillary urothelial neoplasm of low malignant potential, low grade), <3 cm, and no CIS, one immediate instillation of chemotherapy should be followed by one-year full-dose BCG treatment, or by further instillations of chemotherapy for a maximum of one year. In patients with high-risk tumours, defined as a T1 tumour, a high-grade tumour, CIS or multiple, recurrent and large (>3 cm) TaG1G2/LG tumours, a full-dose intravesical BCG for one to three years is indicated. The additional beneficial effect of the second and

TABLE 2. Effect of systemic immune therapy on treatment outcome in transitional cell carcinoma.

Author/Study (Reference)	Line of treatment	N° pts	Control arm	Experimental arm	Results
Rosenberg (12)	2	315	Phase II	atezolizumab	ORR:10%
Balar/ IMvigor210 (13)	1	119	Phase II	atezolizumab	ORR: 23%
Sharma/ CheckMate 032 (14)	2	86	Phase II	nivolumab	ORR: 24.4%
Sharma/ CheckMate 275 (15)	2	265	Phase II	nivolumab	ORR: 28.4%
Massard (16)	2	61	Phase II	durvalumab	ORR: 31%
Plimack/ KEY-NOTE-012 (17)	2	33	Phase Ib	pembrolizumab	ORR: 26%
Bellmunt/ KEY-NOTE-045 (18)	2	542	Phase III Paclitaxel, docetaxel, vinflunine	pembrolizumab	Median OS: 7.4 vs 10.3 mo; HR 0.73; p=0.002

N°: number; pts: patients; ORR: overall objective response rate; OS: overall survival; mo: months; HR: hazard ratio for death.

third years of maintenance should be weighed against its added costs and inconvenience.

BCG treatment induces a local (e.g., cystitis, haematuria) and general toxicity (e.g., fever, asthenia), leading to discontinuation of treatment in 36.1% of the patients. Severe side effects are observed in less than 5% of patients and are the result of systemic absorption of BCG with a generalised infection. Therefore, BCG treatment is contraindicated in patients with congenital or acquired immune deficiency (e.g., human immunodeficiency virus infection, treatment with immunosuppressive agents like anticancer drugs or corticosteroids), in case of active tuberculosis, prior radiotherapy to the bladder, a bladder perforation or an acute urinary tract infection. BCG should not be administered to patients with an allergy to its constituents or used in lactating women.[9]

METASTATIC TRANSITIONAL CELL CARCINOMA

Two classes of drugs that are able to interfere with the interaction of the tumour cells and the immune system have been recently developed:

- monoclonal antibodies against CTLA-4, that inhibit the interaction between the APCs and the T cells (e.g., ipilimumab, tremelimumab);
- monoclonal antibodies against PD (e.g., nivolumab, pembrolizumab, pidilizumab) and PDL (e.g., PD-L1 atezolizumab, durvalumab, avelumab, BMS935559) that inhibit the inactivation of cytotoxic T cells by the tumour cells.

Phase II trials have been performed with these agents (*Table* 2) and were the basis for the registration of atezolizumab, an inhibitor of PD-L1 and pembrolizumab and nivolumab, inhibitors of PD1, for the treatment of patients with metastatic TCC progressing after a platinum-based chemotherapy for metastatic disease, while pembrolizumab can be used in patients not eligible for cisplatin-containing chemotherapy.[10]

These drugs induced an objective response rate, the primary end point of these studies, of more than 20% and atezolizumab treatment resulted in a median progression-free survival of 2.7 months and a median overall survival of 15.9 months.[11-17]

Several phase III trials are studying the effect of these agents on overall survival. One of these trials, comparing standard second-line chemotherapy consisting of docetaxel, paclitaxel or vinflunine with fixed dose pembrolizumab every three weeks in patients failing first-line platinum-based chemotherapy, showed an overall survival benefit of 2.9 months (7.4 versus 10.3; hazard ratio for death, 0.73; p=0.002). The safety profile was in favour of immunotherapy with fewer treatment-related adverse events of any grade and of grade 3, 4, or 5 severity in the pembrolizumab arm compared to the chemotherapy arm (15.0% versus 49.4%).[18]

Most of the studies were performed in unselected patients with TCC. However, when the expression of PD-L1 was studied in tumour tissue, response rates were higher in those patients with a higher expression of PD-L1 compared to those with lower expression and this may be used as a predictive marker, if these data are confirmed in the phase III setting. However, there is lack of standardisation of the determination of PD-L1 expression, which was determined on

KEY MESSAGES FOR CLINICAL PRACTICE

1. Immune modulation has a place in selected subsets of patients with transitional cell carcinoma.
2. Bacillus of Calmette-Guérin immunotherapy is indicated in patients with high-risk localised transitional cell carcinoma.
3. Patients with metastatic transitional cell carcinoma and failing first line platinum-based chemotherapy are candidates for immunotherapy.
4. Predictive markers are being explored and may help patient selection for systemic immunotherapy.
5. Side effects should be closely monitored in patients treated with immunotherapy.

immune cells in the atezolizumab studies, on tumour cells in the nivolumab studies and on both in the studies with pembrolizumab.

FUTURE USE OF IMMUNOTHERAPY

Several trials are running to study the use of these agents as first-line treatment in the metastatic setting, either alone or in combination with other agents, in the adjuvant setting in patients with high-risk TCC, and in patients with non-muscle-invasive TCC after failing BCG treatment.[10]

The value of immunotherapy in this setting should be determined in randomised phase III trials compared with standard treatment.

CONCLUSION

Immune therapy has a longstanding place in the treatment of localised high-risk TCC, and recently interference with the PD receptor system has been registered in the use of metastatic TCC after failing platinum-based therapy based on response rates. We are awaiting the results of phase III trials to see its influence on overall survival.

Other indications of immune therapy in the treatment algorithm of TCC are being explored and may change clinical practice in the near future.

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