Emerging concepts in urothelial cancer

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SUMMARY

Treatment for urothelial cancer has undergone rapid change. Cisplatin based chemotherapy should be given in the neo-adjuvant setting in muscle invasive bladder cancer and could play a role in trimodality therapy when combined with surgery and radiotherapy. Genetic profiling has differentiated several subtypes of urothelial cancer, mimicking progress seen in breast cancer. Of these subtypes, p53 like tumours are less likely to respond to neo-adjuvant chemotherapy. In metastatic urothelial cancer, systemic immunotherapy (checkpoint inhibitors) has shown promising results in first line and second line patients. In a phase III trial, pembrolizumab, an anti-PD1 (programmed cell death 1) antibody, showed a survival benefit in second line metastatic urothelial cancer and should be the new standard of care. In patients who are cisplatin ineligible checkpoint can be used in first line, but no phase III data are available.

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INTRODUCTION

These are exciting times for all specialities with an interest in urologic oncology, in particular for oncologic urologists and medical oncologists. In the last decade, treatment of advanced and metastatic renal cell carcinoma has changed dramatically with targeted agents (tyrosine kinase inhibitors) and more recently with immunotherapy targeting the programmed cell death pathway (checkpoint inhibitors). Urothelial cancer (UC) treatment was lagging behind and treatment options were limited to neo-adjuvant or adjuvant cytostatic in muscle-invasive and palliative chemotherapy in metastatic UC. This has changed: new agents have widened the treatment landscape in UC. As renal cell cancer, UC induces high immunological responses. In fact, UC has the longest standing use of immunotherapy with bacillus Calmette-Guérin (BCG) in non-muscle-invasive bladder cancer (NMIBC). Recent advances in the understanding of cellular immunity introduced new classes of therapeutic agents, modulating the interaction between regulatory T-cells (Treg) and cancer cells. For example, monoclonal antibodies targeting the programmed cell death 1 (PD1) and programmed cell death ligand (PDL1) can induce an effective immune response against cancer cells in diverse cancer types. Several phase II and phase III trials have shown benefit in UC.

This review focuses on the systemic treatment of muscle-invasive (MIBC) and metastatic bladder cancer and upper urothelial tract cancer (UTUC). The first part summarises the modern systemic neo-adjuvant and adjuvant treatment of MIBC. The second part focuses on genetic profiling as emerging predictive and prognostic markers. The third part discusses the recent advances in systemic treatment of locally advanced and metastatic UC.

PART I: NEO-ADJUVANT AND ADJUVANT TREATMENT OF MIBC

Radical cystectomy and extended pelvic lymph node dissection is the gold standard treatment of MIBC.[1] However, survival rates after surgery alone are somewhat disappointing,

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with 5-year overall survival (OS) of 50-60% and cancer specific survival (CSS) of 60-70%, with stage and lymph node status as the most important prognostic factors.[2-4] In recent years, multimodality treatment has been widely researched in MIBC to improve survival rates or as an alternative to radical cystectomy.[5,6]

The use of neo-adjuvant chemotherapy (NAC) was introduced in the 1980s. The theoretical benefits of NAC are a lower burden of micrometastatic disease at the point of initiation of systemic therapy, prognostic information regarding chemosensitivity and better tolerability compared with the post-surgery setting. NAC does not increase surgical complications.[7] Potential delay of curative treatment in non-responders does not seem to impact survival and can be avoided using multi-parametric MRI before and during NAC.[8-10] Several large phase III randomised trials were conducted, which differed in set-up, regimen used, number of cycles and patient selection. In one of the clearest randomised trials, Grossman *et al.* showed a clear benefit in the group receiving the combination of NAC and cystectomy compared with cystectomy alone.[11] Pathological complete responses (pCR) (38% vs 15%) and median OS (77 vs 46 months) improved significantly using a combination of methotrexate, vincristine, doxorubicin and cisplatin (MVAC). The largest meta-analysis performed by the Advanced Bladder Cancer Meta-analysis Collaboration was published in 2005 and showed a 5% absolute OS advantage with cisplatin-based combination (MVAC and CMV) NAC.[12] It is important to note that the combination of gemcitabine and cisplatin (GC) only showed a similar pCR (as intermediary endpoint) to MVAC in retrospective trials and that no randomised prospective trials have been performed using GC.[13] A short course of only four cycles of two-weekly MVAC (dose dense or accelerated MVAC) limits delay to cystectomy and has shown high pCR rates and good safety profiles in prospective phase II trials.[14,15] Pathological downstaging after NAC seems to be a good predictor of survival in MIBC.[16] NAC is often overlooked in smaller and organ confined MIBC (cT2 cN0). Taking into account that one third to over half of bladder cancers are understaged and the fact that T2 patients were included in the randomised control trials, which did not show a differential effect of clinical T stage, T2 tumours should be offered NAC.[12,17] The greatest limiting factor of NAC is renal function, half of the patients are ineligible for cisplatin-based combination chemotherapy and should not be offered NAC.

In the adjuvant setting, chemotherapy always seemed a weaker option compared with NAC. The early stoppage of trials and patients not receiving allocated treatments or not receiving salvage chemotherapy in the control arms have impeded clear guidelines on adjuvant chemotherapy.[18] The EORTC 30994 trial aimed to compare immediate versus deferred cisplatin-based adjuvant chemotherapy in high risk (pT3-4 or N+) patients.[19] The trial recruited poorly, immediate treatment did prolong progression free survival but no significant improvement in 5-year OS was observed. A recent German retrospective observational study did show an improvement in OS and CSS in 224 UTUC patients, but in the adjuvant setting prospective data is still lacking.[20]

Systemic chemotherapy can be part of so called trimodality treatment (TMT). TMT is the combination of transurethral resection of muscle invasive bladder cancer (TURB), chemotherapy (neo-adjuvant and/or concurrent) and radiotherapy and is a possible alternative to radical cystectomy in selected patients.[21] The superiority of concurrent chemoradiotherapy to radiotherapy has been established.[21,22] Cisplatin is the preferred radiosensitiser but adds toxicity. Alternative regimens are mitomycin C plus 5-fluorouracil or gemcitabine. In a phase II trial, concurrent gemcitabine and hypofractionated radiotherapy was well tolerated and showed a CSS of 82% at three years in T2 bladder cancer.[23] Ideal candidates for TMT are fit elderly patients (>75 years) with good bladder function, cT2 and cT3a disease, absence of carcinoma in situ and pathological complete TURB.[24] A recent systematic review concluded that TURB followed by chemoradiotherapy has a 5-year OS of 56% and a bladder sparing rate of 42%.[25] Salvage cystectomy in recurrent invasive disease can be performed with acceptable complication rates and can result in good quality of life in the longterm.[26,27] Recent retrospective data indicates that OS differences still favour RC versus TMT, especially in patients with hydronephrosis and in younger patients.[28] The debate still continues as another meta-analysis showed no difference in OS, CSS or progression free survival between RC and TMT.[29] Neobladder reconstruction is underused in this setting, compliance is very important in follow-up (reTURB at 6-8 weeks) and before administering TMT, patients should be counselled accordingly. NAC has a unique benefit in TMT, as it can distinguish between chemosensible and chemoresistant tumours before a decision is made on final treatment. An intriguing option is currently researched combining NAC with cystectomy followed by adjuvant radiotherapy.[30]

Conclusive data from large randomised trials adding NAC to TMT is lacking because of the belief of physicians in their 'preferred' treatment (cystectomy or radiotherapy) but also some patients' preference toward bladder preservation therapy.[31] Modern guidelines do offer TMT as an alternative to cystectomy in selected well-informed and compliant patients, especially for whom cystectomy is not an option.[1]

Both in the neo-adjuvant and adjuvant setting, half of patients will not be able to receive cisplatin-based combination

chemotherapy due to renal impairment. Although carboplatin is often used in the locally advanced or metastatic setting (see part III), no trials exist showing a benefit of carboplatin in the adjuvant setting.

Trials evaluating neo-adjuvant immunological therapies in other solid tumours have reported encouraging results. There is no reason why this would not be the case in UC. Three trials are currently evaluating checkpoint inhibition in the neo-adjuvant setting: an early phase I study using the anti-PDL1 antibody durvalumab in combination with anti-CTLA-4 tremelimumab (NCT02812420) and two phase II trials evaluating the anti-PD1 antibody pembrolizumab (NCT02736266) and the anti-PDL1 antibody atezolizumab (NCT02451423).

Imvigor010 (NCT02450331) is a very interesting phase III trial comparing observation to adjuvant atezolizumab in high-risk, cisplatin ineligible patients, currently recruiting patients.

PART II: THE GENOMIC REVOLUTION

As in breast cancer, UC can be divided into different clinical entities using gene expression profiling (GEP). Choi *et al.* proposed three different groups with astonishingly large similarities to breast cancer gene profiles: basal, luminal and 'p53-like'.[32] Basal MIBC were, like their breast cancer counterparts, more aggressive at presentation, showed *p53* activation and squamous and sarcomatoid dedifferentiation and were often metastatic at diagnosis. Luminal MIBC were enriched with papillary features, contained activating alterations common in non-MIBC (PPAR-gamma and oestrogen receptor activation) and were high in activating *FGFR3* mutations, potentially targeted by *FGFR* inhibition. The *p53*-like MIBC showed resistance to neo-adjuvant chemotherapy, and all chemotherapy resistant tumours adopted a *p53*-like phenotype after therapy.

In a prospective (neo-)adjuvant trial using MVAC, basal MIBC had improved survival compared to luminal and *p53*-like tumors.[33] *P53*-like tumours were associated with bone metastases at a later stage and resistance to cisplatin-based chemotherapy. The chemotherapy-sensitive basal subtype is more sensitive to immune checkpoint blockade and *EGFR* inhibition in pre-clinical models.[6] Luminal MIBCs, in addition to being enriched with activating *FGFR3* mutations, are enriched with activating *ERBB2* and *ERBB3* mutations, which could lead to interesting (anti-HER2) treatment options.[33,34]

A multinational collaboration, part of The Cancer Genome Atlas project, identified genetic alterations leading to potential therapeutic targets in 69% of UC patients.[35]

Micropapillary urothelial cancer is an aggressive subtype with an aggressive clinical course and a high rate of metastasis to regional lymph nodes and distant organs. GEP identified micropapillary MIBC as an evolution of the luminal subtype with activation of *miR-296* and *RUVBL1* target genes.[36]

Heritable genes in urothelial cancer have not been studied extensively. As an exception, the mismatch-repair pathway (MMR, e.g., MSH2) is typically associated with UTUC and hereditary non-polyposis colorectal cancer (also called Lynch Syndrome). These germ line alterations are common in early onset colon cancer, and up to 28% of carriers will develop UTUC.[37] Patients with Lynch Syndrome should be screened for UTUC. In a study recently presented by Carlo *et al.*, 22% of 113 patients with UTUC carried germ line mutations.[38] Most germline mutations were found in the DNA damage response genes (58%) and less in the MMR genes (31%).

PART III: IMMUNOTHERAPY IN METASTATIC AND LOCALLY ADVANCED UROTHELIAL CANCER

In metastatic (M1) or locally advanced inoperable (T4b and/or N2-3), first line treatment is combination chemotherapy with a platinum compound (cisplatinum) with gemcitabine.[39] However, about half of the patients are unfit for cisplatinum therapy due to poor performance status (PS), impaired renal function or co-morbidities. Median survival is low, around 14 months, and toxicities are common. Until recently, no good second line therapy existed and cytostatic chemotherapy in second line has poor outcomes, both in overall response rate (ORR) and OS.[40] A strong rationale exists for using immunotherapy in UC. In NMIBC, intravesical instillation of bacillus Calmette-Guérin (BCG) is considered standard of care.[41] UC possesses one of the highest mutational burdens, and should be highly antigenic, encouraging trials investigating cytokine and gene therapy, oncolytic viruses and vaccine therapy.[42,43]

The PD1/PDL1 pathway is one of the pathways exploited by tumour cells to escape immune surveillance.[44] PDL1 expressed on tumour cells transmits immuno-inhibitory signals through the PD1 receptor on regulatory T-cells. This interaction inhibits T-cell activation, proliferation, survival and other effector functions of the anti-cancer immune response and is essential in the mechanism of self-tolerance in the human body. Thus, through expression of PDL1 in the tumour microenvironment, solid tumours may elude immune surveillance and eradication.

Pembrolizumab is a highly selective anti-PD1 monoclonal antibody with significant activity in a variety of solid tumours and has been reimbursed in lung, melanoma and kidney cancer. Keynote O45 was a large open label international phase III trial comparing pembrolizumab with chemotherapy of choice in recurrent or progressive UC after cisplatinum based chemotherapy.[45] Pembrolizumab significantly improved OS

KEY MESSAGES FOR CLINICAL PRACTICE

1. All eligible muscle-invasive bladder cancer MIBC patients should receive neo-adjuvant cisplatinum based chemotherapy
2. Classic cytostatic chemotherapy could be included in trimodality therapy in the curative setting.
3. Genomic profiling can be predictive of treatment response and could open urothelial cancer to various new therapeutic possibilities.
4. The introduction of checkpoint inhibitors has changed the treatment landscape in urothelial cancer. Pembrolizumab and other checkpoint inhibitors are first choice in second line therapy in metastatic and locally advanced urothelial cancerUC.
5. In the neo-adjuvant setting several trials are ongoing, especially in the cisplatinum ineligible subgroup of patients.

by approximately three months (10.3 vs 7.4 months), with a lower rate of treatment-related adverse events.

Pembrolizumab also showed good results in a phase I trial in cisplatin ineligible patients (KEYNOTE 052) recently discussed at the ASCO 2017. In this group of patients with very limited treatment options, pembrolizumab produced durable responses and a response rate around 30%. An interesting phase I/II trial (NCT02826564) uses the combination of pembrolizumab with stereotactic body radiotherapy in metastatic UC, investigating possible synergistic anti-cancer immune effects.[46]

In a large phase II trial with 270 patients, another anti-PD1 antibody, nivolumab, showed objective responses in almost 20% of patients in second line setting.[47] IMvigor210 was a large phase II trial with atezolizumab in metastatic UC, at which 310 patients previously treated with platinum-based chemotherapy received atezolizumab. An ORR of 15% and a median OS of 7.9 months was observed.[48] However, phase III results (IMvigor211) failed to show an OS benefit for atezolizumab compared with second line chemotherapy of choice. As for pembrolizumab, first line results in cisplatinum ineligible patients are promising.[49]

Durvalumab is an anti-PDL1 monoclonal antibody that also showed a meaningful clinical effect in previously treated metastatic UC patients with an ORR of 31%, especially in tumours with high (>25%) PDL1 expression (ORR 46.4%).[50]

Various trials have included possible biomarkers to differentiate different groups with higher and lower possibility of response to immunotherapy. Results, however, have not been consistent and no clear biomarker cut-off is ready for prime time in UC immunotherapy.

CONCLUSION

As in other solid tumours, the introduction of checkpoint inhibitors has changed the treatment landscape in UC. As clear phase III trial results are preferred, pembrolizumab seems to be the new first choice in second line therapy in metastatic and locally advanced UC. In the neo-adjuvant setting, several trials are ongoing, especially in the cisplatinum ineligible subgroup of patients. Classic cytostatic chemotherapy could be included in trimodality therapy in the curative setting. Genomic profiling can be predictive of treatment response and could open UC to various new therapeutic possibilities. These are interesting times, indeed.

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ERRATUM

In the article 'Highlights in genito-urinary cancers' by T. Vermassen and S. Rottey published in the ASCO Special of the Belgium Journal of Medical Oncology 2018;12(4):189-195, it was stated that erdafitinib was approved by the FDA based on the phase II BLC2001 study. This is not the case. There was confusion with the granting of Breakthrough Therapy Designation for erdafitinib in urothelial cancer by the FDA, which happened in March 2018, and which was mentioned by the presenting author during the ASCO presentation.