ADVANCES IN MEDICAL TREATMENTS FOR GENITOURINARY CANCERS

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ABSTRACT

Genitourinary (GU) cancers are amongst the most common cancer types, especially neoplasms of the prostate, bladder and kidney. While cure can often only be achieved surgically at early stages, management of advanced or metastatic disease requires systemic medical treatment. With the exception of testicular cancers, systemic therapy of GU cancers has a palliative character and aims to prolong survival and to increase quality of life. With the emergence of molecular targeted therapies such as receptor tyrosine kinase or checkpoint inhibitors, medical management of GU cancers has seen a dramatic progress within the last decade. Moreover, novel combinatorial and sequential therapies have been established thus providing more options for each individual patient but also rendering medical management of urologic tumors more complex. Finally, much progress has been achieved in deciphering the molecular landscapes of GU cancers by next generation sequencing, and novel biomarkers are under investigation to improve patient selection and to optimize systemic therapy.

Key words: Prostate cancer, kidney cancer, bladder cancer, chemotherapy, immunotherapy

INTRODUCTION

Medical management of urologic malignancies has dramatically changed over the last decade. The introduction of novel substances has improved therapeutic possibilities but has also made clinical-decision making in uro-oncology more complex. With the emergence of targeted immunotherapy (*checkpoint inhibitors*) which were highlighted as the major advance of the year 2017 by the American Society of Clinical Oncology (ASCO), a new class of drugs entered the field of urology.

The introduction of molecular characterization of tumors in recent years using whole transcriptome gene arrays or next-generation sequencing has generated large datasets leading to a new understanding of the genomic landscape of genitourinary (GU) cancers (1). These advances may lead to the identification of novel biomarkers predicting response to therapy as well as druggable targets, and may finally translate into a more tailored approach to the management of cancer patients in uro-oncology.

In this review we will summarize recent developments and discoveries in medical treatment of urological cancers, with a focus on prostate, bladder and kidney cancer.

UROTHELIAL CANCER

Radical cystectomy (RC) is the standard of care for muscle invasive urothelial cancer. However, almost 50% of the patients with muscle invasive disease develop metastases within 2 years after surgery (2). The chemotherapeutic agent of choice for first line therapy is cisplatin, usually embedded in a regimen combined with gemcitabine due to lower toxicity compared to a combination with methotrexate, vinblastine and doxorubicin (MVAC) resulting in a median survival of 12-16 months (3). However, 30- 50% of patients are ineligible for cisplatin because of poor performance status, renal impairment or other comorbidities. These patients may receive carboplatin-based chemotherapy exhibiting inferior survival rates of about 9.3 months (4).

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As second-line treatments, mainly vinflunine and paclitaxel are used with marginal benefit over best supportive care (5) highlighting the need for novel therapies.

MODERN IMMUNOTHERAPY CAN BE A GAME CHANGER IN METASTATIC UROTHELIAL CANCER

Immunotherapy has a long history in the treatment of non-metastatic urothelial cancer of the bladder (UCB). In 1976 Alvaro Morales firstly used attenuated mycobacteria as an intravesical therapy of UCB (6). In the following decades a variety of studies could demonstrate a significant impact of Bacillus Calmette-Guérin (BCG) resulting in a decrease of recurrence and progression of localized UCB. Despite all recent progress, BCG remains an established treatment method for patients with non-invasive high-grade UCB.

With the approval of novel immunotherapeutics, a new class of players has entered the field to battle advanced cancer. So-called immune checkpoint proteins are localized on the membrane of T lymphocytes and regulate both activation and inhibition of the immune response. One of the most important regulatory pathways is the interaction between PD-1 the B7.1 receptors and its ligand PD-L1. Tumor cells have the ability to express checkpoint proteins in order to inhibit T-cell mediated immune response. Immune checkpoint inhibitors target the inhibitory signaling pathways between tumor cell and T-cell. This leads to unmasking of tumor cells and their recognition by the immune system and finally resumption of T-cell activity to induce destruction of tumor cells (7). In principle, two different types of monoclonal antibodies are currently applied or clinically investigated for the treatment of GU cancers: PD-1 targeting antibodies such as pembrolizumab and nivolumab or anti-PD-L1 antibodies, atezolizumab, durvalumab or avelumab.

Atezolizumab is a monoclonal anti-PD-L1 antibody that has been approved as a second line therapy after platin-based chemotherapy and as first-line therapy in patients unfit for cisplatin. In the IMvigor-210 trial, a single-arm, multicenter, phase 2 trial, two patient cohorts were investigated (8,9). Cohort 1 comprised patients ineligible for cisplatin while cohort 2 included patients in a second-line setting after platinum-based chemotherapy. Criteria precluding application of cisplatin were glomerular filtration rate lower than 60ml/min, ECOG performance status ≥2, at least grade 2 hearing loss or neuropathy and heart failure NYHA class III or higher. The overall response rate (ORR) in 119 patients in cohort 1 was 23.5% and the overall survival (OS) was 15.9 months. In cohort 2 (310 patients) the ORR was 15% and the median OS was seven months. In a subgroup with higher PD-L1 expression overall response rate was 26% and median OS was 11 months. Surprisingly, it was announced in a press release that the IMvigor 211 phase 3 study comparing atezolizumab with chemotherapy (vinflunine, paclitaxel or docetaxel) in patients with metastastic UCB as second line therapy did not meet its primary endpoint of improved OS. ORR were 13% in both treatment arms. However, median duration of response (DOR) was longer in the atezolizumab arm with 21.7 months compared to 7.4 months in the chemotherapy arm. Grade 3-4 adverse events occurred about as twice as often in the chemotherapy arm compared to atezolizumab (43% vs. 20%). The most common adverse events were fatigue, asthenia, loss of appetite and diarrhea (10). The full publication data are awaited to draw further conclusions.

Pembrolizumab is a humanized monoclonal PD-1 antibody and was approved for second line therapy after chemotherapy and also as a first line immunotherapy for patients unable to receive cisplatin. The Keynote-052 study was a phase 2 single-arm open label study including 370 cisplatin-ineligible patients. 24% of patients showed a response, and 83% of responses were ongoing after 5 months of follow-up. The most common grade 3 or 4 treatment-related adverse events were fatigue (2%), alkaline phosphatase increase (1%], colitis, and muscle weakness (1%) (11).

The phase 3 study (Keynote-045) compared pembrolizumab against conventional chemotherapy (docetaxel, paclitaxel, vinflunine) in 542 patients after platinum-based chemotherapy (12). Patients treated with pembrolizumab had an ORR of 21.1% and a longer median OS compared to chemotherapy (10.3 months versus 7.4 months). Patients in the pembrolizumab arm had a 27% lower risk of death and there were significantly less grade 3 or higher adverse events compared to chemotherapy (15.0% versus 49.4%).

Other checkpoint inhibitors approved for second-line therapy of metastatic UCB are the anti-PD-1 antibody ***nivolumab*** the anti-PD-L1 antibodies ***avelumab*** and ***durvalumab***.

All substances were approved following single arm phase 2 studies. The CheckMate-275 study included 270 patients with metastatic UCB second-line setting. Patients treated with nivolumab showed an ORR of 19.6% and a median OS of 10.3 months (13). Data for avelumab was recently published in a phase 1b study including 44 patients receiving avelumab as a second-line treatment. After a median follow-up of 16.5 months, the ORR was 18.2% while the median duration of response was not reached. The median OS was 13.7 months

with a 12-month survival rate of 54.3%. Avelumab was generally well tolerated (14). The approval of durvalumab was based on a phase 1/2 study including 61 patients. After pretreatment with chemotherapy, ORR was 31 %, up to 46.4% in a subgroup with high PD-L1 expression and 0% in the PD-L1 negative subgroup (15). Updated results of 103 patients after a median follow-up of 7.3 months were presented at the ASCO 2017 meeting. The ORR was 20.4% and responses were seen in both PD-L1 positive and PD-L1-negative tumors, although response rates differed (ORR 29.5% in PD-L1 high compared to 7.7% in PD-L1 low/ negative tumors). Nevertheless, the rates of complete responses were comparable between groups (4.9% in PD-L1 high compared to 5.1% in PD-L1 low/ negative tumors). Median time to response 1.4 months and responses were durable. The median OS was 14.1 months (16).

In the clinical setting, checkpoint inhibitors have the potential to fill a gap in the treatment of patients with advanced or metastatic UCB showing good response rates, better tolerability and safety profile compared to chemotherapy. Especially in patients unfit for cisplatin the introduction of checkpoint inhibitors represents a major advance. Patients responding to checkpoint inhibitors have a chance for durable responses. Nevertheless, although immune-related side-effects of a higher grade are rather rare, they can be severe and potentially life-threatening. Management of patients under immunotherapy may therefore require multi-disciplinary care to handle side-effects.

MOLECULAR BIOMARKERS MAY PREDICT RESPONSE TO CHEMO- OR IMMUNOTHERAPY

To date, there is no reliable method for the prediction of response to chemotherapy. This results in overtreatment and might render patients in a deteriorated physical condition without the opportunity for additional, alternative therapy.

The introduction of molecular characterization of tumors in recent years using next-generation sequencing has generated large datasets leading to a new understanding of the genomic landscape of urothelial carcinoma (UC). With reliable clinical markers missing to discriminate a response to chemotherapy or immunotherapy, molecular characterization holds great promise to identify and select only those patients who benefit most from chemotherapy and spare predictable non-responders from unnecessary cytotoxic side effects.

Several independent groups have identified intrinsic molecular subtypes of UCB. There is a general consensus that gene expression patterns in UCB can roughly discriminate between basal and luminal cancers (17), expressing markers corresponding to less differentiated basal and terminally differentiated cell phenotypes in normal urothelium, respectively.

Choi and colleagues generated two whole transcriptome datasets in patient cohorts comprising 73 and 57 muscle-invasive UCB, respectively. They discriminated basal-like, luminal-like and a subset of tumors with an active p53 gene expression signature ("p53-like") (18). Basal-like tumors had the poorest prognosis in this classification. Interestingly, none of the seven p53-like tumors in the discovery cohort treated with cisplatin-based neoadjuvant chemotherapy (NAC) responded to treatment. In a later study the authors confirmed that most p53-like tumors were chemotherapy-resistant. In contrast, about 50% of the basal-like tumors responded and were pathologically downstaged by NAC.

These results were corroborated by Seiler et al. (19) who assembled several retrospective cohorts to perform whole transcriptome profiling on 343 TURB specimens before NAC. The authors analyzed the subtype-specific survival rates and compared them to a cross-cohort comparison with published datasets of patients undergoing cystectomy without NAC. The authors showed that NAC downstaged and improved OS mainly in patients with basal tumors, but not in tumors of the other molecular subtypes. Notably, basal subtype was the most significant factor to predict chemotherapy-response, while pathological response was not predictive. These results indicate that molecular subtyping may help to identify patients with basal-likes tumors and prioritize them for chemotherapy.

A series of other studies performing mutation analysis have collectively identified better outcome of platinum-based NAC in tumors with deleterious DNA repair mechanisms, specifically mutations in DNA Damage Repair (DDR)-associated genes such as ATM, RB1, BRCA and ERCC2 (and potentially the receptor tyrosine kinase ERBB2) (20). These mechanisms may also work in palliative chemotherapy. Teo et al. investigated 34 DDR-associated genes in a cohort of 100 patients. A total of 47 of the 100 patients harboured at least one DDR gene mutation. Patients with DDR gene alterations receiving platinum-based chemotherapy had a significantly longer progression free survival (PFS) (9.3 versus 6.0 months) and OS (23.7 versus 13.0 months) compared with patients with wild-type DDR genes (21).

In immunotherapy, overall response rates (ORRs) usually do not exceed 30% and the phenomenon of hyperprogression of tumors under checkpoint inhibition has been reported (22). Biomarkers for prediction of therapy response would therefore significantly improve clinical management.

Molecular expression of PD-1 or PD-L1 by tumor cells or T cells has been under investigation as a biomarker to predict response to therapy but seems to play a minor role in predicting response to therapy with atezolizumab, nivolumab or pembrolizumab (8,9,12,13).

Cancers with higher rates of somatic mutations were shown to respond better to immunotherapy (23). The Cancer Genome Atlas (TCGA) ranks UCB as the third highest mutated cancer after melanoma and lung carcinoma (1,24). This translates into higher neoantigen burden playing a role in tumor cell recognition by infiltrating lymphocytes and subsequently to better response to immunotherapy (25).

The correlation of mutational load with survival and response to atezolizumab in patients with UC was examined in the IMvigor 210 study. The authors could indeed show that higher mutational load was associated with significantly better response rates (cohort 1&2) and longer OS (cohort 1) (9).
Further prospective validation with larger sample sizes, homogeneous chemotherapy/ immunotherapy regimens and longer follow up are required to establish molecular evaluation for clinical decision-making.

PROSTATE CANCER

CHAARTED, STAMPEDE AND LATITUDE: NOVEL COMBINATION THERAPIES IMPROVE OUTCOMES IN HORMONE-SENSITIVE PROSTATE CANCER (HSPC)

For decades, androgen deprivation therapy (ADT) has been the standard of care for metastatic HSPC. Chemotherapy or secondary hormonal therapy was restricted for castration resistant prostate cancer (CRPC). In 2014, this doctrine has dramatically changed since the first publication of the CHAARTED (NCT00309985) and the STAMPEDE (NCT00268476) trials in 2014, showing that the upfront combination treatment of docetaxel-based chemotherapy with ADT significantly improves OS in patients with HSPC (26,27). The first study on the combination of ADT plus docetaxel was the prospective randomized GETUG (Genitourinary Group) -AFU-15 study indicating an advantage in PFS and a trend towards longer OS which was, however, not statistically significant (58.9 vs. 54.2 months) (28). The CHAARTED trial was the first to show a significant survival advantage for a combined hormone chemotherapy in metastatic HSPC (26). In the CHAARTED study, ADT was randomized and compared to ADT plus a maximum 6 cycles of docetaxel chemotherapy (75 mg / m², 3-weekly). The results of the study show a statistically significant advantage in terms of progression-free survival and OS (57.6 vs. 44.0 months, hazard ratio 0.61) in favor of combined hormone chemotherapy. Distinction was also made between the metastatic load, whereby the "high volume disease" was defined as ≥4 bony metastases (at least one metastasis outside the spine / bony pelvis) and/or visceral metastases. For patients with a high tumor burden the study found a highly significant survival advantage of 17 months (49.2 vs. 32.2 months, hazard ratio 0.6). In the subgroup of patients with low tumor burden the median survival in both arms was not yet reached (26).

The STAMPEDE trial also showed a survival advantage for ADT plus Docetaxel compared to ADT alone in HSPC (27). In this multi-arm study patients with locally advanced prostate cancer, patients progressing after primary curative local therapy or patients with primary metastatic prostate cancer were included. The study could demonstrate an advantage in OS of 10 months (77 vs. 67 months, hazard ratio 0.76) in favor of combined hormone chemotherapy compared to mono ADT. A subgroup analysis indicated that patients without distant metastases did apparently not benefit from hormone chemotherapy. In the subgroup of metastatic disease (61% of patients) OS was 22 months longer in favor of combined chemotherapy (65 vs. 43 months, hazard ratio 0.73).

In 2017 the results of two studies on the combination of androgen deprivation plus abiraterone/ prednisone in metastatic HSPC were published at the same time (29,30). In both studies, the addition of abiraterone plus prednisone to conventional ADT resulted in a significant benefit in PFS and OS, comparable to those with hormone chemotherapy with docetaxel. The LATITUDE trial included patients with newly diagnosed, high-grade metastatic HSPC (with ≥2 of the factors: Gleason score ≥8, ≥3 lesions in the bone scan or measurable visceral lesions). The median PFS was 14.8 vs. 33 months (hazard ratio 0.47) and OS was 34 months vs. not reached (hazard ratio 0.62) in favor of a combination therapy with ADT+abiraterone/ prednisone (29).

The STAMPEDE study included patients with metastatic HSPC and patients with relapse after previous curative local therapy (prostatectomy, radiation therapy). They equally showed a benefit of a combination therapy ADT+abiraterone/ prednisone compared to ADT monotherapy with a treatment failure free survival of 80 vs. 62 months (hazard ratio 0.40) (30).

Based on the results of the LATITUDE and STAMPEDE studies it is expected that the international guidelines will soon include the recommendations for the combination of ADT+abiraterone / prednisone as an alternative to ADT+docetaxel-based chemotherapy in advanced or metastatic HSPC. Especially

in patients with a poor performance status, therapy with abiraterone/prednisone may be a viable option. However, it remains currently unclear which patient may benefit more from the one or the other combination therapy.

IMMUNOTHERAPY IS STILL IN ITS INFANCY IN PROSTATE CANCER

In the treatment of prostate cancer, vaccination of therapy called Sipuleucel-T was found to be effective in metastatic castration-resistant prostate cancer and has been approved by the FDA (31). However, the promising clinical data for second-line treatment with checkpoint inhibitors in renal cancer and UCB have not yet been transferred to metastatic prostate cancer. The studies to date have provided rather disappointing results: in a Phase 3 study, the anti-cytotoxic T-lymphocyte antigen-4 (CTLA4) antibody ipilimumab was compared with placebo in 799 patients with metastatic castration-refractory prostate cancer (mCRPC) after radiotherapy. Although a longer PFS was observed in the ipilimumab arm (4.0 vs. 3.1 months, p <0.0001), no significant benefit for the OS could be demonstrated after a mean observation period of 12 months (11.2 vs. 10.0 months, p=0.053) (32). In a recent phase 3 study, 400 patients with chemo-naïve mCRPC were treated with ipilimumab versus placebo. There was even a tendency for a worse OS in patients treated with ipilimumab compared with placebo (28.7 vs. 29.7 months) (33). One explanation for these disappointing results may be the rather low rate of tumor-infiltrating lymphocytes and the low mutational load in prostate cancer compared to other tumors (25).

RENAL CANCER TARGETED THERAPIES ARE EFFECTIVE IN RENAL CANCER

In renal cancer 'classic' immunotherapy using interleukin-2 and interferon was the therapy of choice for metastatic renal cancer until the mid-2000's. However, survival and response rates were poor and side-effects were high (34). The era of targeted therapy began in 2007 with the approval of sunitinib for metastatic renal cancer (mRC). Since then, a variety of receptor tyrosine kinase inhibitors and, recently, also immunotherapy with nivolumab was approved. Thus, more than ten substances are currently available for the treatment of mRC.

In the *first-line setting* the choice of therapy is based on the MSKCC or IMDC - ("International Metastatic Renal Cell Carcinoma Database Consortium"-) Criteria (35). For patients with a clear cell mRC and a favorable or medium risk profile sunitinib, pazopanib and the combination of bevacizumab and IFN- are recommended as first-line therapies. The COMPARZ study compared pazopanib vs. sunitinib in mRC and showed similar oncological outcomes. The median PFS here was 8.4 month for pazopanib vs. 9.5 months for sunitinib-treated patients. Median OS was 28.4 months in the pazopanib, compared to 29.3 months in the sunitinib group (36). In case of an unfavorable prognosis (poor risk) therapy with the mTOR (mammalian target of rapamycin) inhibitor temsirolimus is recommended (37).

Therapy options for *second-line* treatment include the tyrosine kinase inhibitor (TKI) axitinib (after prior sunitinib therapy), sorafenib, pazopanib, everolimus and lenvatinib plus everolimus as options. Several guidelines highlight the TKI cabozantinib and the checkpoint inhibitor nivolumab as preferred second-line substances because they showed an advantage in OS (37).

The phase 3 METEOR study published in 2015 compared the effectiveness of cabozantinib against everolimus as a second-line therapy in mRC. The median PFS was significantly longer for cabozantinib with 7.4 months compared to 3.8 months in the everolimus arm. The objective response rates were 21% for cabozantinib and 5% for everolimus. An interim analysis for the data of the OS revealed a survival advantage of 33% for cabozantinib. In the final analysis this advantage was confirmed with a median OS of 21.4 months in the cabozantinib and 16.5 months in the everolimus arm (38). Worth mentioning at this point are the results of the phase II study CABOSUN published in 2016. In this randomized phase 2 study, cabozantinib was compared against sunitinib in a first line setting in patients with intermediate or poor risk mRC. Treatment with cabozantinib significantly prolonged median PFS by 8.2 compared to 5.6 months with sunitinib. In addition, there was a reduction by 34% (hazard ratio 0.66) in the progression and mortality rate for cabozantinib (39).

Nivolumab was approved for mRC based on the results of the phase 3 CheckMate 025 study in November 2015 (40). The CheckMate 025 study included 821 patients with an advanced or mRC, pretetrated with one or already several antiangiogenic therapeutics. The ORR was higher with nivolumab than with everolimus (25% vs. 5%). Nivolumab significantly prolonged OS compared to everolimus (25.0 vs. 19.6 months, respectively) whereas PFS was comparable on both treatment arms (nivolumab 4.6 vs. everolimus 4.4 months). In intermediate or poor risk patients nivolumab showed an ORR of 25%. 31% of those patients had a durable response for more than 12 months. Patients receiving nivolumab had a 27% lower risk of dying (from any cause).

Adjuvant therapy

In November 2017 sunitinib was approved by the FDA for the adjuvant treatment of patients after nephrectomy with a high risk for recurrence. The approval was based on the placebo-controlled, double-blind S-TRAC trial including a total of 615 patients following nephrectomy (41). Median disease-free survival (DFS) for patients taking sunitinib was 1.2 years longer compared to placebo (6.8 vs. 5.6 years, hazard ratio 0.76; p=0.03). At the time of analysis, OS data were not mature. In higher risk patients, the median DFS was 6.2 versus 4.0 years for sunitinib and placebo, respectively (hazard ratio 0.74, p=0.04). Grade 3/4 adverse events (AEs) were experienced by 63.4% of patients in the sunitinib group compared with 21.7% in the placebo arm. Adjuvant therapy has to be seen critical as the benefit on PFS was rather poor and OS data are still missing.

CONCLUSIONS AND FUTURE DIRECTIONS

The introduction of immune-checkpoint inhibitors targeting the PD-1/PD-L1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) pathways has changed the treatment landscape of GU cancers significantly. Modern immunotherapeutics showed effectiveness and tolerable safety profiles, especially in renal cancer and UCB. However, ORRs usually do not exceed 30% and the phenomenon of hyperprogression of cancers under treatment with PD-1/PD-L1 inhibition with subsequent worsened prognosis has been reported (22). It becomes more evident that 'one size does not fit all' in cancer therapy and that only subpopulations of patients respond to a certain therapy, independently of the choice of substance. Through research efforts we are beginning to understand the underlying molecular mechanisms. A first step is to identify and then implement biomarkers for prediction of therapy response which would significantly improve clinical management. Despite tremendous efforts to identify predictive genetic and molecular characteristics of response these potential biomarkers have not yet translated into clinically established tools. All published studies on biomarkers for prediction of response to chemotherapy have important limitations such as the small number of patients and the heterogeneity of chemotherapy regimens. However, ongoing clinical trials examining the benefit of individual therapies by molecular patient selection hold promise to shed light on this question. As an example, the COXEN trial (NCT02177695) using a co-expression extrapolation analysis to assess the use of biomarkers for treatment personalization in UCB is awaited. Clinical implementation of useful biomarkers for urological tumors is therefore awaited within the next years.

But what can we offer patients not responding to therapy? We will certainly learn that each tumor has its own molecular characteristics and we do not deal with one tumor but many. Potentially, future implementation of molecular characterization will lead to individualized cancer treatments, so called precision medicine. Molecular tumor boards may present a standard procedure in a few years' time.

Personalized cancer therapy is dependent on analysis of tumor specimens. However, tumor characteristics may change significantly during therapy and in fact a recurrent tumor may present completely different characteristics compared to the primary tumor (18). Nevertheless, biopsies may not be available because surgical resection of metastasis is not always feasible or safe. Recently, several groups have purified and characterized circulating, cell-free tumor DNA from body liquids, such as serum (42). So-called liquid biopsies offer a convenient way to determine changes in the presence of tumor burden, the genotype and phenotype during therapy or follow-up. Liquid biopsies may lead to a non-invasive real-time monitoring of tumor disease and provide a rationale for clinical-decision making.

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