Oncological topics presented at EAU 2018

MARCH 16-20, COPENHAGEN, DENMARK

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SUMMARY

At the occasion of the Annual Congress of the European Association of Urology (EAU), a number of new trial protocols with new immuno-oncology drugs were presented for bladder and renal cancer next to the results of studies on adjuvant and neo-adjuvant chemotherapy for upper tract transitional cell carcinoma. In prostate cancer, the value of prostate-specific antigen screening and multiparametric MRI at first diagnosis was investigated, and the results of clinical trials with enzalutamide and apalutamide were reported.

(BELG J MED ONCOL 2018;12(7):339-341)

RENAL CELL CANCER

In metastatic renal cell cancer, programmed cell death (PD)-1 inhibitors have been shown to be active and should therefore be investigated as a new therapy in the adjuvant setting. Dr. T. Powles presented the KEYNOTE-564 study, a phase III, randomised, double-blind trial of pembrolizumab, as adjuvant treatment of renal cell carcinoma after nephrectomy. In the inclusion criteria, clear cell type, intermediate to high risk of recurrence, no evidence of metastatic disease and no prior systemic therapy are withheld. In the trial, 950 patients should be enrolled and are randomised for 200 mg pembrolizumab or a placebo every three weeks. The study is recruiting in around twenty countries, not only in Europe and North America but also in Asia, Australia and South America.[1]

BLADDER CANCER

Also in bladder cancer, immunotherapy is currently investigated either in monotherapy or in combinations. The ARCADIA trial, presented by dr. D. Raggi *et al.*, evaluates cabozantinib and durvalumab in an open-label, single-arm, multicentre, phase II trial for advanced chemotherapy-pre-treated bladder carcinoma.[2]

On the other hand, KEYNOTE-057, presented by dr. J. Bellmunt *et al.*, aims at recruiting 260 patients with non-muscle-invasive high-grade and bacillus Calmette-Guérin-unresponsive bladder cancer receiving 200 mg pembrolizumab every three weeks for 24 months. Enrolment is ongoing in Asia, Australia, Europa, North and South America.[3]

Dr. T. Powles also presented KEYNOTE-361 that evaluates pembrolizumab with or without chemotherapy versus chemotherapy alone in patients with advanced metastatic urothelial carcinoma. Chemotherapy consists of cisplatin or carboplatin + gemcitabine. This study is also actively recruiting in 22 countries.[4]

An important practice changing clinical trial about adjuvant platinum-based chemotherapy for upper tract urothelial cancer was presented by dr. AJ Birtle. This British POUT study investigated whether adjuvant chemotherapy can improve the disease-free survival for patients with invasive or node positive upper tract transitional cell carcinoma (pT2-pT4-pN0-3 M0 or pT any, pN1-3, M0). In the trial, 261 patients

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Conflict of interest: The author has nothing to disclose and indicates no potential conflict of interest.

Keywords: bladder cancer, diagnosis, prostate cancer, renal cell cancer, treatment.

were randomised for chemotherapy (cisplatin or carboplatin and gemcitabine) or supportive care.

The proportion of patients that were alive and relapse free at two years was 0.71 in the chemotherapy arm versus 0.54 in the surveillance arm (p=0.001). Adjuvant platinum-based chemotherapy should be considered a new standard-of-care in these patients.[5]

Obviously, also neo-adjuvant chemotherapy was tested for locally advanced upper tract urothelial cancer by dr. Y. Kubota *et al.* In five centres, 426 patients undergoing radical nephro-ureterectomy were examined retrospectively (1995-2017). Of those patients, 43% had neo-adjuvant chemotherapy (platin-based) and gemcitabine. Pathological downstaging was obvious in the treatment arm, and the authors found a prolonged recurrence free and cancer specific survival. Neo-adjuvant chemotherapy was an independent predictor for recurrence free and cancer specific survival but not statistically significant for overall survival. Further prospective studies will need to confirm a clinical benefit of this treatment approach.[6]

Finally, in bladder cancer, precision selection for immunotherapy was presented at the plenary session by dr. T. Powles. Patients with overexpression of the biomarker PD-L1 have a higher likelihood of responding to the treatment and also have a prolonged survival. PD-L1 thus has shown to be prognostic but not predictive. The studies presented so far with atezolizumab, avelumab, durvalumab, nivolumab and pembrolizumab have used different antibodies for immunohistochemistry testing, and the inconsistencies in the biomarkers highlight the weakness of the data available. Therefore, one needs to look at a second generation of biomarkers. Bladder cancer has a high mutational burden, and this is why immunotherapy seems to work so well (as well as in lung and kidney cancer and melanoma).[7]

PROSTATE CANCER

Prostate-specific antigen (PSA)-based screening results in a significant PCa mortality reduction, but the European Randomized study of Screening for Prostate Cancer (ERSPC) has a relatively short follow-up, and PSA contamination may have impacted on the results. Dr. D. Osses *et al.* performed a pilot study in The Netherlands in 1,153 men to see what screening does over a longer time follow-up.

The men were aged 55-74 years and randomised to screening (49%) or control (51%). PSA testing was done every four years, the upper age limit was 74 years. In men with PSA above ≥3.0 ng/ml, a biopsy was done. The median follow-up was extended (19 years). Prostate cancer specific mortality was the primary endpoint. In the screening arm, three men were detected with metastasis compared to eight men in the control arm. In the screening arm, seven men progressed to metastatic disease compared to fourteen in the control arm. This means an overall relative risk reduction of 0.53 in favour of screening. The authors conclude that PSA-based screening reduces PCa-specific mortality and metastatic disease. The major harm of PSA-based population screening is overtreatment that today can be dramatically reduced by the introduction of multiparametric MRI, the application of active surveillance and the use of PSA density and PSA velocity next to total serum PSA.[8]

Dr. C.N. Sternberg presented the results of the PROSPER study, investigating the metastasis-free survival in patients receiving enzalutamide or placebo on continued androgen deprivation therapy (ADT) in a randomised, double-blind, placebo controlled study of 1,401 men with asymptomatic M0 castrate-resistant prostate cancer (CRPC). Enzalutamide significantly increased the metastasis-free survival compared to placebo (p<0.0001), and that arm delivered also of a greater proportion of men with PSA responses, 10% of them reaching undetectable levels.[9]

Apalutamide in combination with androgen deprivation therapy was compared with placebo and ADT in a randomised 2:1 trial, presented by F. Saad in 1,207 patients with non-metastatic CRPC. The health-related quality of life (HrQoL) was assessed by validated questionnaires and showed that HrQoL was maintained while the median metastasis-free survival at two years was increased. The authors suggest that apalutamide + ADT is potentially the new standard-of-care in non-metastatic CRPC.[10]

Oligometastatic PCa has become a formerly unknown clinical entity since the introduction of modern imaging (MRI and PET-CT). Poulsen *et al.* reported on 210 patients that were scheduled for treatment of the primary tumour and underwent a blinded choline PET/CT. After un-blinding, eighteen patients showed to be oligometastatic. A quarter of patients who received curative intended treatment had less biochemical recurrence and developed less castration-resistant disease, and none of them died. These findings suggest that curative intended treatment of the primary tumour matters in oligometastatic prostate cancer.[11]

Finally, an extremely important study on the benefits of multiparametric MRI was presented by the PRECISION study group. Up to now, the EAU guidelines advocate the use of multiparametric MRI after a first set of negative prostate puncture biopsies in clinically or biochemically prostate cancer suspicious men. The PRECISION study was a prospective, randomised, non-inferiority trial carried out in 25 centres allocating 500 men to either a 10-12 core TRUS biopsy or to an MRI with or without targeted biopsies (TB). The detection of clinically significant prostate cancer was significantly higher

KEY MESSAGES FOR CLINICAL PRACTICE

1. Invasive and node positive upper tract transitional cell carcinoma should be treated with adjuvant chemotherapy.
2. Prostate-specific-antigen-based prostate cancer screening reduces prostate cancer specific mortality and metastatic disease.
3. Patients with asymptomatic castrate-resistant prostate cancer fare better with enzalutamide than with a placebo.
4. Apalutamide + androgen deprivation therapy potentially is the new standard-of-care in non-metastatic castrate-resistant prostate cancer.
5. Treatment of the primary tumour could improve the outcome in oligometastatic prostate cancer.
6. Patients that are suspect to have prostate cancer, best first undergo an MRI.

in the MRI group. MRI with TB diagnosed fewer men with insignificant cancer ($p<0.001$) avoiding overdiagnosis (and thus overtreatment). The application of multiparametric MRI upfront in men carrying the risk of having prostate cancer, implies that fewer men are biopsied, fewer biopsy cores are taken and that a greater number of significant cancers is diagnosed with a lower risk of diagnosing insignificant cancer.[12]

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