L'Institut Servier Annual Scientific Sessions

19th Colloquium 2019
Revolutions in cancer treatment:
how can they be integrated?

Urological cancers

Philippe Beuzeboc
Department of Medical Oncology and Supportive Care, Hôpital Foch, Suresnes, France

Springer Healthcare

Abstract

The molecular classification of urological cancers is now making it possible to implement more and more targeted treatment strategies based on molecular biomarkers. In 2019, three new marketing authorisations were issued for combinations of drugs to treat clear cell renal cancer that are superior to the recommended standard. In prostate cancer, the discovery of abnormalities in DNA repair genes has led to successful testing of poly-(ADP-ribose)-polymerase (PARP) inhibitors, either alone or in combination with new hormone therapies. Finally, the recent molecular classification of bladder cancer has made it possible to develop new treatment strategies, such as the use of pan-fibroblast growth factor receptor (FGFR) inhibitors or antibodies conjugated with cytotoxic agents.

CLEAR CELL RENAL CANCER

Until about 2016-2017, the therapeutic landscape in clear cell renal cell carcinoma (RCC) consisted of anti-angiogenic treatments (sunitinib, bevacizumab, sorafenib, pazopanib, axitinib), mammalian target of rapamycin (mTOR) inhibitors (temsirolimus, everolimus), and a treatment targeting vascular endothelial growth factor (VEGF)/Met/AXL pathways (cabozantinib). The first immunotherapy (nivolumab) then appeared, and in 2018, combinations of immunotherapies, such as nivolumab plus ipilimumab, showed more significant effects than sunitinib in terms of overall survival in patients with advanced clear cell RCC in the CheckMate 214 study.[1] Due to these results, the European Society for Medical Oncology (ESMO) recommended this combination in high-risk and intermediate-risk forms of the disease.

Two new combinations of anti-angiogenic treatments and immunotherapies arrived in 2019. Two therapeutic trials, JAVELIN 101 and KEYNOTE-426, showed that combinations of avelumab plus axitinib and pembrolizumab plus axitinib, respectively, were more effective than sunitinib monotherapy.[2, 3] A recent editorial compared the three trials,[4] which showed superiority in terms of overall survival for nivolumab plus ipilimumab and axitinib plus pembrolizumab, and superiority in terms of progression-free survival for avelumab plus axitinib. There are reasonable grounds for optimism in view of these initial results, which have shown, in the case of nivolumab plus ipilimumab, a 9% complete response rate for metastatic disease that was previously resistant to all treatments. However, it is necessary to consider the adverse effects of these combinations, which may also cause significant toxicity.

We are now seeing a real revolution; no less than three new marketing authorisations were registered in 2019, complicating the process of updating recommendations and managing the reimbursement of new treatments. Over the course of 2 years, we now have three new drugs that are more effective than standard treatment, making implementation of the recommendations difficult. In addition, the recommendations from the two European bodies may differ, since ESMO does not yet incorporate combinations of anti-angiogenic agents with immunotherapies, while the European Association of Urology (EAU) does.[5] Clearly, this impacts recommendations on second-line treatment, which are determined on the basis of what is used as a first-line drug.

WHAT PROGRESS CAN BE EXPECTED IN METASTATIC CLEAR CELL RENAL CANCER?

Data will soon be available from a French phase II trial (BIONIKK, NCT02960906). The results should make it possible to design treatment strategies based on four different signatures of gene expressions derived from a panel of 35 genes (*Ccrcc1*: cold immunogenic tumour, *Ccrcc2*: angiogenic signature, *Ccrcc3*: normal expression of genes in the kidney, and *Ccrcc4*: inflammatory phenotype). The main aim of the BIONIKK study is to evaluate the objective response rate (ORR) based on the molecular groups and the treatment allocated (nivolumab as monotherapy, nivolumab combined with ipilimumab or a tyrosine kinase inhibitor such as sunitinib or pazopanib). It should be possible to establish when treatment with immunotherapy is indicated and when it is not using the patient's genetic signature.

PROSTATE CANCER

Significant progress has been made in metastatic castration-resistant prostate cancer (mCRPC) with the arrival of new hormone therapies, making it possible to improve both survival and quality of life for patients. During treatment with hormone therapy, which is often given for several years, a number of molecular events occur, particularly during the metastatic phase, involving DNA repair genes and the phosphoinositide 3-kinase (PI3K) pathway.[6] In 2015, a transcriptomic analysis sequenced 150 castration-resistant tumours that had already been treated with chemotherapy/hormone therapy to discover new molecular targets.[7] The mutations and amplifications seen were most commonly located on the androgen receptor. About 20% of advanced-stage prostate cancers presented with abnormalities in the DNA repair genes (e.g. *BRCA1, BRCA2, RAD51*), and at least one-third of patients showed a loss of function of the phosphatase and TENsin homolog (*PTEN*) gene. Identifying these targets opens up the possibility

of new therapeutic approaches, such as the use of PARP or AKT inhibitors or entry pathways into the cell cycle. One randomised phase II trial, for example, has shown the value of combining an AKT inhibitor, ipatasertib, with a new hormone therapy, such as abiraterone, for patients with *PTEN* deletion.[8] Recruitment for the phase III trial is complete and the results should be available in 1 or 2 years.

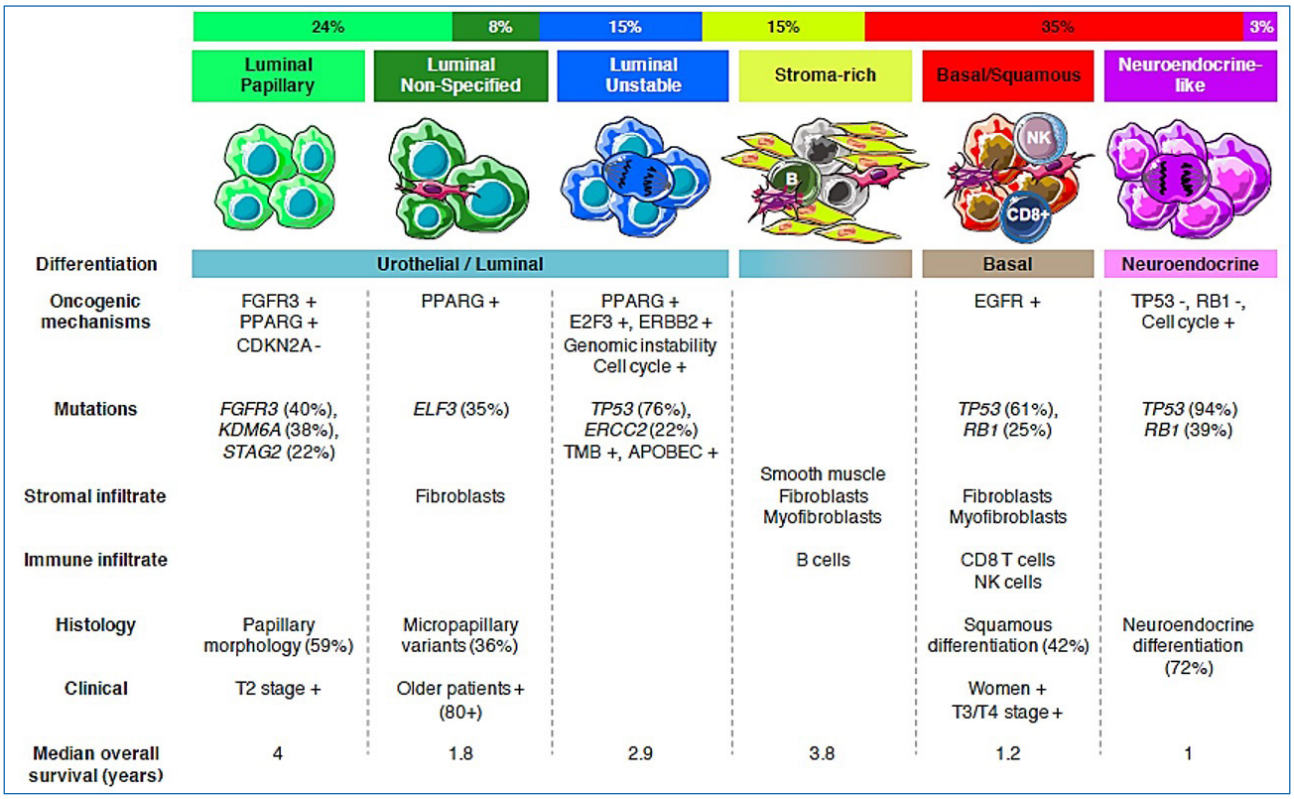
The key discovery of genetic profiling in mCRPC has been the very high percentage of cases with abnormalities in DNA repair genes. One study collected sequencing data to investigate germ-line mutations in 20 DNA repair genes associated with a syndrome of predisposition to autosomal dominant cancers. These data came from 692 patients in 8 institutions who were affected by documented prostate cancer, but who were not selected based on family history. Eighty-four germ-line mutations in 16 genes were identified in 82 men (11.8%).[9] Overall, 44% of the abnormalities involved *BRCA2*-type repair genes, making these cancers possible candidates for treatment with PARP inhibitors, which are increasingly used in ovarian and breast cancers. A phase II therapeutic trial involving 50 multi-treated patients with mCRPC showed that olaparib had anti-cancer activity in the 20–30% of cases with a DNA repair abnormality (De Bono et al, oral communication at the ASCO-GU, 2020). Although next generation genome sequencing is not yet available in routine clinical practice, the promising early data provide a rationale for identifying patients with DNA repair abnormalities so that they can be included in clinical trials of personalised treatments. Further trials are, of course, needed, though a number of PARP inhibitors (olaparib, rucaparib, talazoparib, niraparib) have now been tested, either alone or in combination with new hormone therapies. Some interesting results have already been obtained in mCRPC with PARP inhibitors combined with immunotherapy.[10]

In the PROfound trial, tumours from 2792 patients with mCPRC were sequenced to investigate abnormalities in DNA repair genes.[11] The results showed frequent (27.9%) alterations in DNA repair genes in patients with metastatic prostate cancer, with 8.7% involving *BRCA2* (as compared with 1.2% in the general population); prostate cancer with *BRCA2* mutations disproportionately affects young patients. In the PROfound trial, olaparib was compared with new hormonal agents (enzalutamide or abiraterone) in two groups: (1) men with mutations in BRCA1, BRCA2 or ATM, and (2) men with defects in a range of 12 other DNA repair genes that are less commonly involved. The results were unequivocal – in the cohort with alterations in the *BRCA1, BRCA2* or *ATM* genes, median progression-free survival was 7.39 months on olaparib compared with 3.55 months on hormonal treatment. A trend towards improved overall survival was observed, but the final analysis is still pending. This is the first phase III trial specifically addressing prostate tumours with a targeted molecular alteration. These data show that, as with breast and lung cancers, prostate cancer is not a single disease, but rather a group of multiple different diseases. Therefore, we must also begin to identify the genomic profile of different groups of patients so that we can treat them with a suitable targeted therapy.

BLADDER CANCER

The molecular classification of urothelial cancers has recently been completed,[12] no doubt making it possible to provide more targeted treatments on the basis of genomic abnormalities (**Figure 1**). Immunotherapies are currently being offered as a second line of treatment for metastatic urothelial cancers. In the United States, five drugs (atezolizumab, avelumab, durvalumab, nivolumab and pembrolizumab) are registered for this indication. In France, the KEYNOTE-045 study was the pivotal trial for obtaining marketing authorisation for pembrolizumab in patients with advanced urothelial cancer that recurred or progressed after platinum-based chemotherapy. The initial results showed an overall median survival of 10.3 months in the pembrolizumab arm (200 mg every 21 days) versus 7.4 months in the chemotherapy arm (paclitaxel, docetaxel or vinflunine). The overall survival benefit was eventually confirmed, with a final overall median survival of 10.3 months as compared with 7.3 months, with median follow-up of 27.7 months.[13, 14]

Figure 1. Molecular classification of urothelial cancers.
Adapted from Reference [12]: Eur Urol 77:420-33, Kamoun et al. Bladder cancer molecular taxonomy group. A consensus molecular classification of muscle-invasive bladder cancer. © 2020 with permission from Elsevier.



Alterations in the fibroblast growth factor receptor (FGFR) family are common in urothelial carcinomas (20–25%), particularly mutations of *FGFR3,* which are primarily found in luminal tumours (up to 30%). Erdafitinib is an oral pan-FGFR inhibitor (inhibiting FGFR 1–4), which has been tested in a phase II trial in 99 patients with advanced or metastatic tumours harbouring alterations of *FGFR*. These patients were treated continuously with erdafitinib at a dose of 8 mg/day with the option of titrating up to 9 mg/day. The results showed an overall response rate of 40%, including 3% of patients with complete response (which could be long-term) with a total of 76% of patients showing reduction in tumour size.[15] This type of targeted therapy is therefore particularly relevant today to maximise efficacy in bladder cancer. The first results from BISCAY (NCT02546661), a phase 1b trial comparing the combination of immune therapy plus targeted therapeutic inhibitors (FGFR1, 2, and 3, PARP, TORC 1 + 2) with PD-L1 monotherapy group (durvalumab), also showed response rates of 20–36% in patients with specific mutations receiving targeted treatment. These data raise interesting questions about future strategies for the treatment of metastatic urothelial carcinomas.

Finally, encouraging results have been seen with conjugated antibodies such as enfortumab vedotin.[16, 17] Enfortumab vedotin consists of a monoclonal antibody targeting nectin-4, which is conjugated to the microtubule inhibitor auristatin E via a linker. Nectin-4 is a transmembrane cellular adhesion molecule that is strongly expressed in urothelial cancers (93%). After the antibody binds to the receptor, the whole complex is internalised and the cytotoxic drug is released within the cell. A phase I dose escalation and expansion study was carried out in 112 patients with metastatic urothelial cancer who were treated with a dose of 1.25 mg/kg, and showed an overall response rate of 41% (with 4% complete response rate) and a median response duration of 5.75 months. Furthermore, when pembrolizumab is combined with enfortumab vedotin, almost all the patients respond to treatment. Further research is underway with another conjugated antibody, sacituzumab govitecan.[18]

In the future we will have several new treatments for bladder cancer, which until now has very much been a 'poor relation' in oncology. It should be remembered that prior to the recent progress, no new drugs had been approved in bladder cancer for 25 years.

REFERENCES (Underlined references link to PubMed abstracts)

[1] Motzer RJ, Tannir NM, McDermott DF, Aren FO, Melichar B, Choueiri TK et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018;378:1277-90.
[2] Motzer RJ, Penkov K, Haanen J, Rini B, Albiges L, Campbell MT et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380:1103-15.
[3] Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380:1116-27.
[4] Escudier B. Combination therapy as first-line treatment in metastatic renal-cell carcinoma. N Engl J Med 2019;380:1176-8.
[5] Ljungberg B, Albiges L, Abu-Ghanem Y, Bensalah K, Dabestani S, Fernandez-Pello S et al. European Association of urology guidelines on renal cell carcinoma: the 2019 update. Eur Urol 2019;75:799-810.
[6] Nava RD, Rescigno P, Liu D, Yuan W, Carreira S, Lambros MB et al. Immunogenomic analyses associate immunological alterations with mismatch repair defects in prostate cancer. J Clin Invest 2018;128:4441-53.
[7] Robinson D, Van Allen EM, Wu YM, Schultz N, Lonigro RJ, Mosquera JM et al. Integrative clinical genomics of advanced prostate cancer. Cell 2015;161:1215-28.
[8] de Bono JS, De GU, Rodrigues DN, Massard C, Bracarda S, Font A et al. Randomized phase ii study evaluating akt blockade with ipatasertib, in combination with abiraterone, in patients with metastatic prostate cancer with and without PTEN loss. Clin Cancer Res 2019;25:928-36.
[9] Pritchard CC, Mateo J, Walsh MF, De SN, Abida W, Beltran H et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med 2016;375:443-53.
[10] Karzai F, VanderWeele D, Madan RA, Owens H, Cordes LM, Hankin A et al. Activity of durvalumab plus olaparib in metastatic castration-resistant prostate cancer in men with and without DNA damage repair mutations. J Immunother Cancer 2018;6:141.
[11] de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 2020;382:2091-102.
[12] Kamoun A, de Reyniès A, Allory Y, Sjödahl G, Robertson AG, Seiler R, et al, Bladder cancer molecular taxonomy group. A consensus molecular classification of muscle-invasive bladder cancer. Eur Urol 2020;77:420-33.
[13] Bellmunt J, de WR, Vaughn DJ, Fradet Y, Lee JL, Fong L et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017;376:1015-26.
[14] Fradet Y, Bellmunt J, Vaughn DJ, Lee JL, Fong L, Vogelzang NJ et al. Randomized phase III KEYNOTE-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: results of > 2 years of follow-up. Ann Oncol 2019;30:970-6.
[15] Loriot Y, Necchi A, Park SH, Garcia-Donas J, Huddart R, Burgess E et al. Erdafitinib in locally advanced or metastatic urothelial carcinoma. N Engl J Med 2019;381:338-48.
[16] Rosenberg JE, O'Donnell PH, Balar AV, McGregor BA, Heath EI, Yu EY et al. Pivotal trial of enfortumab vedotin in urothelial carcinoma after platinum and anti-programmed death 1/programmed death ligand 1 therapy. J Clin Oncol 2019;37:2592-600.
[17] McGregor BA, Sonpavde G. Enfortumab Vedotin, a fully human monoclonal antibody against Nectin 4 conjugated to monomethyl auristatin E for metastatic urothelial carcinoma. Expert Opin Investig Drugs 2019;28:821-6.
[18] Fenn KM, Kalinsky K. Sacituzumab govitecan: antibody-drug conjugate in triple-negative breast cancer and other solid tumors.Drugs Today (Barc) 2019;55:575-85.