3rd Belgian Multidisciplinary Meeting on Urological Cancers

3rd BMUC, 5 March 2016, Brussels, Belgium

T. Vermassen, MSc[1], R. de Wit, MD, PhD[2], R. van Velthoven, MD, PhD[3], S. Albisinni, MD[3], N. Martinez Chanza, MD[4], F. Aoun, MD[3,5], E. Seront, MD, PhD[6], S. Rottey, MD, PhD[1]

Due to the success of last year, a third national Belgian Multidisciplinary scientific meeting on Urological Cancers was held with the cooperation of medical oncologists (BSMO), urologists (BAU) and radiation oncologists (ABRO/BVRO). It was a great opportunity to build bridges between these three important specialisms involved in the treatment of urological cancers.

The steering committee of the meeting consisted of J.P. Machiels, G. Pelgrims, S. Rottey (members of BSMO), L. Hoekx, S. Joniau, T. Roumeguere (members of BAU), O. De Hertogh, G. De Meerleer and Y. Neybuch (members of ABRO-BVRO). The third meeting, held in La Hulpe, Brussels on March 5th, 2016 was a great success with more than 100 attendees of the different specialisms involved.

In this report of the meeting you can find a summary of the most important lectures given at the symposium.

(Belg J Med Oncol 2016;10(6):232-235)

The role of chemotherapy in prostate cancer

Docetaxel has been available for more than ten years for the treatment of metastatic castration resistant prostate cancer (mCRPC). The overall survival (OS) benefit obtained in the pivotal study TAX 327, comparing docetaxel plus prednisone and mitoxantrone plus prednisone was 2.9 months in the final analysis. Since this survival benefit was obtained despite confounding effects by cross-over to docetaxel in a third of patients failing mitoxantrone, and the benefit in terms of symptom and quality of life improvements during docetaxel treatment is frequently obvious, its use was rapidly adopted. The treatment landscape of mCRPC has changed dramatically over the past few years, with the introduction of several new approved drugs including cabazitaxel, abiraterone, enzalutamide, and radium-223.[1-5] This considerable progress also comes with new challenges. Concerns of cross-resistance between the taxanes (i.e. docetaxel and cabazitaxel) and androgen receptor (AR)-targeted agents have arisen, and the optimal drug treatment sequence is still undetermined. There is increasing evidence, albeit from retrospective studies for clinical cross-resistance of reduced efficacy of docetaxel in men with mCRPC who had previously been treated with abiraterone.

Taxanes act through microtubule interaction and polymerisation inducing mitotic arrest and apoptosis. Recent reports demonstrated that paclitaxel and docetaxel also impair AR-nuclear transport and signalling, which mCRPC might be responsible for part of their therapeutic efficacy.[6-8]

Xenograft studies using human prostate cancer cell lines have cross-resistance between docetaxel and enzalutamide. The overlapping mechanism of action indeed conferred cross-resistance between docetaxel and enzalutamide at a cellular level. In contrast to docetaxel, cabazitaxel remained highly effective in enzalutamide-

[1]Department of Medical Oncology, Ghent University Hospital, Ghent, Belgium, [2]Department of Medical Oncology, University Medical Centrum Rotterdam, Rotterdam, The Netherlands, [3]Department of Urology, Institut Jules Bordet, Brussels, Belgium, [4]Department of Medical Oncology, Erasme Hospital, Brussels, Belgium, [5]Saint Joseph University – Hotel Dieu de France, Beyrouth, Lebanon, [6]Department of Medical Oncology, Cliniques Universitaires St-Luc, Brussels, Belgium.

Please send all correspondence to: S. Rottey, MD, PhD, Ghent University Hospital - 2BII, Department of Medical Oncology, De Pintelaan 185, 9000 Ghent, Belgium, tel: +32 9 332 26 92, fax: +32 9 332 62 85, email: Sylvie.Rottey@UGent.be.

Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Keywords: prostate cancer, seminoma, urothelial bladder cancer.

resistant xenografts, demonstrating greater antiproliferative properties independent of the AR pathway.
Several clinical studies have indeed suggested impaired efficacy of docetaxel in the post-AR therapy setting, whereas the efficacy of cabazitaxel seems to be maintained.[6-9] Two large randomised trials, CHAARTED and STAMPEDE, have shown a robust and clinically meaningful survival benefit by the addition of docetaxel to androgen deprivation therapy in men with hormone-naïve metastatic prostate cancer. The magnitude of the OS in the castrate sensitive setting (13-15 months in the M1 patient population) is much larger than obtained with the use of chemotherapeutic or novel hormonal agents in the setting of mCRPC.[10,11] Consequently, these results should be considered as practice changing in the daily treatment of men with prostate cancer. Men with newly diagnosed hormone-naïve metastatic prostate cancer, who are considered fit to receive chemotherapy, should be offered six cycles of docetaxel in addition to androgen deprivation therapy.[12]

The current role of minimally invasive surgery in the management of urothelial bladder cancer

Open radical cystectomy is the standard of care in the surgical management of muscle-invasive and high-risk non-muscle invasive bladder cancer.[13] Nonetheless, its significant morbidity has pushed urologists to explore the feasibility and safety of laparoscopic and robotic-assisted radical cystectomy.[14,15] Multiple studies have demonstrated the efficacy of the procedure, with generally a reduced blood loss and reduced post-operative complications, although results may suffer from selection bias.[16] Investigators have also explored the long-term oncologic outcomes of minimally invasive cystectomy, and the European Association of Urology – section of Uro-technology (ESUT) has built a large database of patients undergoing laparoscopic radical cystectomy for this purpose.[17] Globally, the oncologic results appear similar to those reported in contemporary open series, with actuarial recurrence free survival, cancer-specific survival and OS rates of 66%, 75% and 62% at five years and 62%, 55% and 38% at ten years; similar data have been also reported by large robotic centers.[17-19] Nonetheless, even if performed respecting the principles of open oncologic surgery, the minimally invasive approach presents a major difference with open surgery, i.e. the pneumoperitoneum. This 'invisible' entity significantly affects physiology and some authors have hypothesised a possible role in tumour cell seeding.[15,20,21] There is rising concern in the urologic community on the impact of the pneumoperitoneum on urothelial bladder cancer dissemination. Investigators have indeed reported increased cases of peritoneal carcinosis and extrapelvic lymphatic spread of cancer cells.[22] Moreover, abnormal metastatic landing sites have been reported. The ESUT published a provoking and in depth analysis of patients presenting early recurrences after laparoscopic radical cystectomy, showing disease progression and abnormal metastases in close to 5% of patients with favourable pathologic characteristics (≤pT2N0R0). A role of the intermittent gas insufflation and squeezing of cancer cells in the Batson's plexus has been hypothesised and requires further investigation.[23] The future of minimally invasive surgery in the management of urothelial bladder cancer lays on this unanswered clinical enigma.

The role of chemotherapy in seminoma

Testicular seminomas are the most common testicular germ cell tumours with increasing incidence over the last decades.
Stage I seminomas represent the majority of testicular germ cell tumour patients. Given the fact that the cure rate for this group is superior to 99% with an overall survival near 100%, minimising late toxicity becomes an important issue. Surveillance is considered the preferred strategy today. When active surveillance is not an option, single agent carboplatin is equally effective. Risk factors for relapse, such as tumour >4 cm and rete testis involvement, need to be prospectively validated. For stage II seminomas a cisplatin-based chemotherapy is highly curative. The combination of carboplatin and radiotherapy has been proposed for stages IIA and IIB, however further studies are warranted. Stages IIC and III require a cisplatin based chemotherapy regimen. High dose chemotherapy is used as a salvage treatment in specialised centres. The exact role of high dose chemotherapy in the management of testicular germ cell tumours is still under evaluation by several ongoing clinical trials.

Prostate cancer highlights from the 2016 ASCO GU Cancers Symposium

The last ASCO GU Cancers Symposium brings the best minds in oncology to San Francisco to discuss the latest advances in prostate cancer care and research. Four interesting studies deserve to be highlighted. Studies on hypofractionation radiotherapy (RT) demonstrated that hypofractionation provides a cost- and resource-effective treatment that is easier and more convenient

Key messages for clinical practice

1. The role of chemotherapy in prostate cancer: Due to an overlap in action mechanisms of taxanes and androgen receptor-targeted agents, there is an increased risk of cross-resistance and reduced efficacy. This has to be further eluded to determine the optimal drug treatment sequence for metastatic castration resistant prostate cancer patients.
2. The current role of minimally invasive surgery in the management of urothelial bladder cancer: Although laparoscopic and robotic-assisted radical cystectomy results in less morbidity and less post-operative complications in comparison to open radical cystectomy, there has been increasing occurrence of disease recurrence and abnormal metastatic sites. Further investigation is warranted.
3. The role of chemotherapy in seminoma: Hence the good survival rates in stage I seminoma, efforts must be made to minimise late toxicity in these patients. For stage II and III seminoma, chemotherapy and radiotherapy appears to offer a good therapeutic approach although further evaluation is warranted.
4. Prostate cancer highlights from the 2016 ASCO GU Cancers Symposium: Hypofractionation radiotherapy is more cost- and resource-effective and non-inferior compared to conventional radiotherapy in low and intermediate risk prostate cancer. Next, adding bicalutamide to salvage radiation therapy following radical prostatectomy improved overall survival. Lastly, more heterogeneous circulating tumour cells are linked to increased resistance to anti-androgen therapy and prostate cancer death.
5. Non-prostate cancer highlights from the 2016 ASCO GU Cancers Symposium: Atezolizumab in monotherapy shows potential as treatment for patients with metastatic urothelial cancer while the combination of ipilimumab with chemotherapy does not. For treatment of metastatic renal carcinoma, both nivolumab and cabozantinib were far superior compared to everolimus and will become a standard as second-line systemic therapy.

for patients. Eagerly awaited results from two phase III randomised controlled trials were released.

The first trial, RTOG 0415, evaluated 1.092 low risk prostate cancer patients. At a median of 5.8 years, hypofractionated RT (28 fractions of 2.5 Gy over 5.6 weeks, for a total dose of 70 Gy) was found to be non-inferior to conventional fractionation (41 fractions of 1.8 Gy over 8.2 weeks) in terms of disease free survival rate: 86% *vs.* 85% (hazard ratio=0.85, 95% CI [0.64–1.14]) shaving off 2.6 weeks.[24]

The second trial, the CHHiP trial, was a three arm trial that included 3.216 intermediate risk prostate cancer patients. It demonstrated that a hypofractionation RT regimen of 60 Gy over four weeks was non-inferior to conventional RT (37 fractions over 7.4 weeks for a total dose of 74 Gy).[25]

The results of another phase III trial, the RTOG 9601 trial, were also presented during the meeting. Adding a course of two years of 150 mg of bicalutamide to salvage radiation therapy following radical prostatectomy improved overall survival and reduced the incidence of metastatic disease and disease-specific mortality compared to RT alone without causing undue toxicity (only gynecomastia). At a median follow-up of 12.6 years, the overall survival rate was 82% in the bicalutamide arm and 78% in the placebo arm for a hazard ratio of 0.75, 95% CI (0.58–0.98).[26]

Finally, researchers from Memorial Sloan Kettering Cancer Centre isolated circulating tumour cells from blood samples of 179 patients with mCRPC. Patients who have a more heterogeneous set of detectable circulating tumour cells were more likely to develop resistance to anti-androgen therapy and to die from their disease.[27]

Non – prostate cancer highlights from the 2016 ASCO GU Cancers Symposium

Atezolizumab has the potential to change the standard of care of metastatic urothelial cancer treatment. In the IMvigor210 phase II trial, patients received the PD-L1 inhibitor atezolizumab after platinum failure. The overall response rate was 15% in the general population but reached 26% (11% complete response) in patients with higher PD-L1 expression. Tolerance was excellent, responses were durable and the twelve month OS was 48%, 30% and 36% in patients with high, moderate and absent PD-L1 expression, respectively.[28]

More disappointing is the association of ipilimumab with chemotherapy in first-line metastatic setting of metastatic urothelial cancer. This combination did not result in overall response rate or OS improvement com-

pared to historical controls.[29]

In metastatic renal carcinoma, second-line therapeutic options are expanding. In the CheckMate025 trial, the anti-PD1 nivolumab showed a significant six month survival advantage over everolimus in previously treated patients, regardless of PD-L1 expression. In the current updated analysis, nivolumab was favoured in all MSKCC risk groups and particularly in the poor-risk group. Nivolumab confers its benefits across the number and sites of metastases and prior therapies.[30]

In a similar setting, the first interim analysis of the METEOR trial showed that the tyrosine kinase inhibitor cabozantinib significantly improved progression-free survival compared to everolimus (7.4 *vs.* 3.8 months), with a strong trend toward improved OS. In the updated analyses, cabozantinib was favoured across all subtypes (risk category, metastatic sites, number and type of prior treatments), appearing even more effective in bone metastasis and in prior treatment with sunitinib or with a checkpoint inhibitor.[31]

References

1. Tannock IF, et al. TAX 327 Investigators: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351:1502-12.
2. de Bono JS, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364:1995-2005.
3. de Bono JS, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376:1147-54.
4. Parker C, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369:213-23.
5. Ryan CJ, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013;368:138-48.
6. Mezynski J, et al. Antitumour activity of docetaxel following treatment with the CYP17A1 inhibitor abiraterone: clinical evidence for cross-resistance? Ann Oncol. 2012;23:2943-7.
7. Schweizer MT, et al. The Influence of Prior Abiraterone Treatment on the Clinical Activity of Docetaxel in Men with Metastatic Castration-resistant Prostate Cancer. Eur Urol. 2014;66:646-52.
8. van Soest RJ, et al. Cross-resistance between taxanes and new hormonal agents abiraterone and enzalutamide may affect drug sequence choices in metastatic castration-resistant prostate cancer. Eur J Cancer. 2013;49:3821-30.
9. Scher HI, et al. Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy. N Engl J Med. 2012;367:1187-97.
10. Sweeney CJ, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med. 2015;373:737-46.
11. James ND, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet. 2016;387:1163-77.
12. Van Soest R, de Wit R. Irrefutable evidence for the use of docetaxel in newly diagnosed metastatic prostate cancer: results from the STAMPEDE and CHAARTED trials. BMC Med. 2015;13:304.
13. Witjes JA, et al. EAU guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2013 guidelines. Eur Urol. 2014;65:778-92.
14. Pruthi RS, et al. Robotic radical cystectomy for bladder cancer: surgical and pathological outcomes in 100 consecutive cases. J Urol. 2010;183:510-4.
15. Huang J, et al. Laparoscopic radical cystectomy with orthotopic ileal neobladder for bladder cancer: oncologic results of 171 cases with a median 3-year follow-up. Eur Urol. 2010;58:442-9.
16. Patel R, et al. Controversies in Robotics: Open Versus Robotic Radical Cystectomy. Clin Genitourin Cancer. 2015;13:421–7.
17. Albisinni S, et al. Long-term analysis of oncological outcomes after laparoscopic radical cystectomy in Europe: results from a multicentre study by the European Association of Urology (EAU) section of Uro-technology. BJU Int. 2015;115:937–45.
18. Raza SJ, et al. Long-term oncologic outcomes following robot-assisted radical cystectomy: results from the International Robotic Cystectomy Consortium. Eur Urol. 2015;68:721-8.
19. Snow-Lisy DC, et al. Robotic and laparoscopic radical cystectomy for bladder cancer: long-term oncologic outcomes. Eur Urol. 2014;65:193-200.
20. El-Tabey NA, Shoma AM. Port site metastases after robot-assisted laparoscopic radical cystectomy. Urology. 2005;66:1110.
21. Carmignani CP, Sugarbaker PH. Regional lymph node metastasis from port site implants after laparoscopic surgery. Surg Endosc. 2004;18:1818.
22. Nguyen DP, et al. Recurrence patterns after open and robot-assisted radical cystectomy for bladder cancer. Eur Urol 2015;68:399-405.
23. Albisinni S, et al. Critical analysis of early recurrences after laparoscopic radical cystectomy in a large cohort by the ESUT. J Urol. 2016;195:1710-7.
24. Lee WR, et al. NRG Oncology RTOG 0415: A randomized phase III non-inferiority study comparing two fractionation schedules in patients with low-risk prostate cancer. J Clin Oncol. 2016;34S2:abstr 1. Presented at the 2016 Genitourinary Cancers Symposium.
25. Dearnaley DP, et al. Comparison of hypofractionated high-dose intensity-modulated radiotherapy schedules for prostate cancer: Results from the phase III randomized CHHiP trial (CRUK/06/016). J Clin Oncol. 2016;34S2:abstr 2. Presented at the 2016 Genitourinary Cancers Symposium.
26. Shipley WU, et al. NRG Oncology/RTOG 9601, a phase III trial in prostate cancer patients: Anti-androgen therapy (AAT) with bicalutamide during and after salvage radiation therapy (RT) following radical prostatectomy (RP) and an elevated PSA. J Clin Oncol. 2016;34S2:abstr 3. Presented at the 2016 Genitourinary Cancers Symposium.
27. Scher HI, et al. Single CTC characterization to identify phenotypic and genomic heterogeneity as a mechanism of resistance to AR signalling directed therapies (AR Tx) in mCRPC patients. J Clin Oncol. 2016;34S2:abstr 163. Presented at the 2016 Genitourinary Cancers Symposium.
28. Hoffman-Censits JH, et al. IMvigor 210, a phase II trial of atezolizumab (MPDL3280A) in platinum-treated locally advanced or metastatic urothelial carcinoma (mUC). J Clin Oncol. 2016;34S2:abstr 355. Presented at the 2016 Genitourinary Cancers Symposium.
29. Galsky MD, et al. Phase II trial of gemcitabine + cisplatin + ipilimumab in patients with metastatic urothelial cancer. J Clin Oncol. 2016;34S2:abstr 357. Presented at the 2016 Genitourinary Cancers Symposium.
30. Motzer RJ, et al. CheckMate 025 phase III trial: Outcomes by key baseline factors and prior therapy for nivolumab (NIVO) versus everolimus (EVE) in advanced renal cell carcinoma (RCC). J Clin Oncol. 2016;34S2:abstr 498. Presented at the 2016 Genitourinary Cancers Symposium.
31. Escudier BJ, et al. Subgroup analyses of METEOR, a randomized phase 3 trial of cabozantinib versus everolimus in patients (pts) with advanced renal cell carcinoma (RCC). J Clin Oncol. 2016;34S2:abstr 499. Presented at the 2016 Genitourinary Cancers Symposium.