The first Belgian multidisciplinary meeting on urological cancers

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The Belgian multidisciplinary meeting on urological cancers was initiated as the first national multidisciplinary scientific meeting of medical oncologists (BSMO), urologists (BAU) and radiotherapists (ABRO-BVRO). It was a great opportunity to build bridges between these three important specialisations involved in the treatment of uro-oncology.

The steering committee of the meeting consisted of J. P. Machiels, G. Pelgrims, S. Rottey (BSMO); L. Hoekx, S. Joniau, T. Roumeguere (BAU); O. De Hertogh, G. De Meerleer and Y. Neybuch (ABRO-BVRO).

The first meeting, held in Brussels on March 29th, 2014 was a great success with more than 150 attendees of the different specialisations involved.

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Stage 1 testicular cancer

Testicular cancer is the most frequent malignancy in young men, with a rising incidence. According to the Dutch cancer registry (IKNL), the incidence in the Netherlands was 336 patients in 1989 and 725 patients in 2011. Approximately two thirds of the patients present with clinical stage I (seminoma and non-seminoma equally divided).

Seminoma testis

Active surveillance is the standard of care for low risk patients. However in the last decades, prophylactic para-aortal radiotherapy (PR) has become an effective therapy in these patients. Even with reduced field and reduced dose (20 Gy) this treatment is effective with a relapse rate of less than 5%, which are similar to these for active surveillance in low risk patients, and an overall survival of nearly 100% after effective salvage treatment.[1,2] However, approximately 80% of patients are treated unnecessarily and there are serious concerns regarding early and late toxicity. The frequently used prognostic factors for relapse of tumour seize >4 cm and tumour ingrowth in rete testis have not been validated in an independent set of patients. Oliver et al. demonstrated that adjuvant chemotherapy with one cycle carboplatin AUC 7 is non-inferior to PR.[1] Risk adapted treatment was studied by the Spanish Germ Cell Cancer Group: patients with zero or one risk factors allocated on active surveillance and patients with two risk factors allocated on adjuvant carboplatin (2 cycles AUC 7). The approach seemed safe and effective.[3] The European Society for Medical Oncology (ESMO) guidelines still consider active surveillance as standard of care.[4] The risk adapted strategy is seen as controversial. Adjuvant chemotherapy (or radiotherapy) may be considered but indicates a risk of overtreatment. Therapeutic decision should be shared with a well informed patient.

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Non-seminoma testis

The most important independent risk factor for relapse is lymphovascular invasion (LVI) that discriminates low risk stage I - in the absence of LVI - with a relapse rate of 15-20% and high risk stage I - in the presence of LVI - with a relapse rate of 40-50%. Surveillance is a well established approach, in low risk patients, with relatively safe and effective chemotherapy at relapse (usually three cycles of BEP) leading to disease specific survival of nearly 100%. Retroperitoneal lymph node dissection (RPLND) is technically demanding and should be performed in experienced centres but is inferior to adjuvant chemotherapy. This approach should be reserved for specific circumstances, such as patients refusing chemotherapy. Adjuvant chemotherapy with one or two cycles of BEP was investigated in several studies and turns out to be safe and effective with relapse rates between 2 and 5%.[5] The ESMO guidelines consider active surveillance standard of care for low risk patients (and chemotherapy at time of relapse). For high risk disease there are two standard options: Surveillance and three cycles of BEP at time of relapse or adjuvant chemotherapy with one or two cycles of BEP, with similar survival for both options. RPLND may be considered in specific cases (teratoma in the primary tumour or contra-indication against surveillance or chemotherapy).[4] Finally, EAU guidelines advise primary chemotherapy for high risk patients, while for low risk patients surveillance may be considered as long as they are compliant and well informed about expected recurrence rates and salvage treatments.[6]

Overview ASCO GU 2014 non-prostate

Testicular cancer

Oxaliplatin has shown a response rate of up to 19% in refractory germ cell tumours (GCT).[7] A multicentre phase II trial has proven that the combination of flavopiridol plus folfox gives a partial response of 50% in late relapse (≥2 years) patients ($p = 0.025$).[8]

Previously, the GETUG 13 trial investigated personalised chemotherapy in poor-prognosis GCT patients.[9] An analysis of relapse events from those patients indicated brain metastases to count for 19% of all first progression events and 48% of all radio-clinical progression events, of which most occurred within the first year of therapy.[10]

Bladder cancer

The number of cystectomies per year in the United Kingdom has risen continuously since 2001. Following an improving outcomes guidance from the National Institute for Health and Care Excellence, cystectomies have been centralised to high volume centres (>50 per year) with decrease of 30 day mortality, one year mortality and number of re-interventions as result.[11]

Renal cell cancer

Retrospective analysis has proven the usefulness of cytoreductive nephrectomy next to tyrosine kinase inhibitors (TKIs) in patients with synchronous metastatic renal cell cancer (RCC) and ≤3 International mRCC Database Consortium risk criteria ($p \leq 0.0024$).[12]

The SWITCH trial reported equal adverse events and treatment efficacy for sorafenib (SO) / sunitinib (SU) versus SU/SO. Second line progression free survival was significantly higher in the SO/SU treatment arm. Although this result is controversial as second line treatment arms were imbalanced and total progression free survival as well as overall survival were similar between both sequential treatments.[13]

The MARS study underlined the importance of renal function follow-up during treatment with TKIs. It was shown that hypertension and proteinuria can already be present in RCC patients at baseline before treatment with TKIs and that 21.4% of the patients developed hypertension and 75% developed de novo proteinuria. Glomerular filtration rate remained similar during TKI treatment.[14]

Finally, lymphopenia (absolute lymphocyte count <1300 cells/μL) can act as a predictor for poor prognosis in papillary RCC patients. Multivariate analysis indicated inferior overall survival compared to patients with absolute lymphocyte count ≥1300 cells/μL (hazard ratio = 2.1 [1.1 – 4.0]; $p = 0.037$).[15]

Overview ASCO GU 2014 prostate

The most anticipated presentation was clearly the release of results of the phase III Prevail study, testing the AR antagonist enzalutamide in the chemotherapy naïve CRPC. Prevail randomised 1.717 patients to enzalutamide or placebo.[16] Enzalutamide significantly reduced the risk of death by 29% (HR 0.706, $p<0.0001$) and delayed mean radiological PFS (HR = 0.186, $p < 0.0001$). The estimated mean rPFS was 3.9 months with placebo (95% CI 3.7 to 5.4) and was not yet reached (NYR) with enzalutamide (95% CI 13.8 to NYR). For both co-primary end points, the results were consistent across pre-specified subgroups (e.g., ECOG 0 or 1, age above or below 75 years, presence or absence of visceral disease and geographic regions).

These results are clearly practice changing and should definitively seal the place of AR pathway inhibitors as first line CRPC agents. In contrast, two other highly anticipated studies, that included Belgian patients, failed to confirm their anticipated benefits. The phase III trial investigating the 17,20-lyaseinhibitor Tak700 enrolled 1.099 CRPC patients. After a mean follow-up time of 10.7 months, the study was terminated for failing to meet its primary end point.[17] The median OS was 17.0 months with Tak700 and 15.2 months with placebo ($p = 0.1898$).

Two study results updates on the treatment of locally advanced PCa are also worth mentioning. An updated analysis of the SPCG Study VII confirmed that adding external beam radiotherapy (EBRT) to a short course LHRH agonist followed by an anti androgen more than halved the 10- and 15-year PCa-specific mortality rates for men with locally advanced prostate cancer, compared to hormone therapy (HT) alone.[18] For the men receiving HT alone, the 10- and 15-year PCa-specific mortality rates were 18.9% and 30.7%, respectively. For those receiving the combination, these rates were 8.3% and 12.4%. This clearly highlights the role of local treatment in non-metastatic PCa. Over the past years, Canadian researchers suggested that in terms of overall and PCa-specific survival, the duration of ADT could be safely reduced from three years to eighteen months as adjuvant to EBRT when treating patients with locally-advanced PCa. This year the authors have presented the quality of life results.[19] The eighteen month ADT group had significantly better results on six out of 21 scales and fourteen out of 55 items. However, the differences were only clinically rele-vant for two of the items (hot flushes and enjoyable sex); none of the differences observed on the scales were deemed to be clinically significant. The debate of a risk/benefit of a shorter duration of ADT is still ongoing.

Conclusion

Active surveillance is used as standard of care in stage 1 seminoma testicular cancer although adjuvant chemotherapy (or radiotherapy) may be considered. Active surveillance is used as standard of care for low risk stage 1 non-seminoma testicular cancer patients and remains an option for high risk patients next to BEP chemotherapy. There is evidence to screen for brain metastases in patients with poor prognosis germ cell tumours, even in the absence of apparent metastatic disease. Current guidelines for treatment of metastatic renal cell carcinoma are still applicable. Enzalutamide in naïve castration-resistant prostate cancer reduced risk of death and delayed mean radiological progression-free survival.

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