Podium Session 4: Bladder and Prostate Cancer
June 30, 2014, 1050-1150

POD-04.01

Enzalutamide in Men with Chemotherapy-naïve Metastatic Prostate Cancer: Results of the Phase 3 PREVAIL Study

Saad, Fred[1]; Gleave, Martin[2]; Joshua, Anthony[3]; Klotz, Laurence[4]; Lacombe, Louis[5]; Beer, Tomasz[6]; Tombal, Bertrand[7]; Noonberg, Sarah[8]; Bhattacharya, Suman[8]; Phung, De[9]; Loriot, Yohann[10]; Evans, Christopher[11]; Armstrong, Andrew[12]; Venner, Peter[13]

[1]Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada; [2]Vancouver Prostate Centre, Vancouver, BC, Canada; [3]Princess Margaret Cancer Centre, Toronto, ON, Canada; [4]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [5]Centre de recherche clinique et évaluative en oncologie, Centre Hospitalier Universitaire de Québec - Hotel-Dieu de Québec, Quebec, QC, Canada; [6]Oregon Health & Science University, Portland, OR, Canada; [7]Cliniques Universitaires Saint-Luc, Brussels, Belgium; [8]Medivation Inc, San Francisco, CA, United States; [9]Astellas Pharma, Leiden, Netherlands; [10]Institut Gustave-Roussy, Villejuif, France; [11]UC Davis Cancer Center, Sacremento, CA, United States; [12]Duke University Medical Center, Durham, NC, United States; [13]Cross Cancer Institute, Edmonton, AB, Canada

Introduction and Objectives: Enzalutamide (enza), an oral androgen receptor inhibitor, improved overall survival (OS) in men with metastatic castrate-resistant prostate cancer (mCRPC) who had received docetaxel. This study examined if enza could prolong OS and radiographic progression-free survival (rPFS) in asymptomatic or mildly symptomatic chemotherapy (chemo)-naïve mCRPC.

Methods: In this randomized, double-blind, placebo (pbo)-controlled, phase 3 study (NCT01212991), chemo-naïve men with mCRPC were stratified by site and randomized 1:1 to enza 160 mg/day or pbo. OS and rPFS were co-primary endpoints and analyzed for the ITT population. Planned sample size was 1680 with 765 deaths to achieve 80% power to detect a target OS hazard ratio (HR) of 0.815 with a type I error rate of 0.049 and a single interim analysis at 516 (67%) deaths. rPFS had sufficient power to detect a target HR of 0.57 and a type I error rate of 0.001 with a minimum of 410 events.

Results: 1717 men were randomized (1715 treated) between September 2010 and September 2012. Interim analysis at 540 deaths showed a statistically significant benefit of enza over pbo with 29% reduction in risk of death (OS: HR 0.71; 95% CI: 0.60-0.84; P< 0.0001) and 81% reduction in risk of radiographic progression or death (rPFS: HR 0.19; 95% CI: 0.15-0.23; p<0.0001). At the time of OS analysis, 28% of enza patients and 35% of pbo patients had died. Median OS was 32.4 months (mo) (95% CI: 30.1-not yet reached [NYR]) in the enza arm vs. 30.2 mo (95% CI: 28.0-NYR) in the pbo arm. Median rPFS was NYR (95% CI: 13.8—NYR) in the enza arm vs. 3.9 mo (95% CI: 3.7-5.4) in the placebo arm. Seizure events were reported in two patients. The Independent Data Monitoring Committee recommended stopping the study and crossing pbo patients to enza. Secondary endpoints and safety analysis will be presented.

Conclusions: Treatment with enza significantly improves OS and rPFS in men with chemo-naïve mCRPC.

POD-04.02

Rates of Complications not Related to Urinary Incontinence or Erectile Dysfunction after Radical Prostatectomy or Radiotherapy for Prostate Cancer

Nam, Robert[1]; Cheung, Patrick[2]; Herschorn, Sender[1]; Saskin, Refik[3]; Su, Jiandong[3]; Klotz, Laurence[1]; Chang, Michelle[1]; Kulkarni, Girish[1]; Lee, Yuna[4]; Kodama, Ronald[1]; Narod, Steven[5]

[1]Division of Urology, University of Toronto, Toronto, ON, Canada; [2]Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada; [3]Institute of Evaluative Clinical Sciences, University of Toronto, Toronto, ON, Canada; [4]Department of Medicine, University of Toronto, Toronto, ON, Canada; [5]Department of Public Health Sciences, University of Toronto, Toronto, ON, Canada

Objectives: To accurately estimate the cumulative rates at 5 years of complications associated with treatment of localized prostate cancer by prostatectomy or radiotherapy.

Methods: We conducted a population-based retrospective cohort study of prostate cancer patients using administrative hospital data, physician billing codes and cancer registry data for men who underwent prostatectomy or radiotherapy alone between 2002 and 2009 in Ontario. Main outcomes were the development of a complication in any of five categories: 1) those requiring hospital admission to manage a treatment-related problem, 2) those requiring a minimally-invasive urological procedure, 3) those requiring a rectal/anal-based procedure, 4) those requiring an open procedure, and 5) the development of a secondary malignancy.

Results: Of 32,465 patients, the 5-year cumulative rate of admission to hospital for a treatment-related complication was 22.2% (95% CI: 21.7%-22.7%), but 2.4% (95% CI: 2.2%-2.6%) for patients whose length of stay was greater than one day. The 5-year cumulative risk of requiring a urological procedure was 32.0% (95% CI: 31.4%-32.5%), of a rectal/anal procedure was 13.7% (95% CI: 13.3%-14.1%) and of an open procedure was 0.9% (95% CI: 0.8%-1.1%). The risk of second primary malignancy from year 5-9 was 3.0% (95% CI: 2.6%-3.5%). Increasing age and comorbidity were important predictors for a complication in all outcome categories, except for open procedures. Treatment type was the strongest predictor. Patients who were treated with radiotherapy experienced higher rates of complications in each category than patients who had RP (adj HRs 1.86 to 5.65, p<0.0001).

Conclusions: Complications after prostate cancer treatment are frequent and dependent on age, co-morbidity and the type of treatment. Patients and physicians should be aware of these risks in addition to the well established effects of urinary incontinence and erectile dysfunction when choosing treatment for prostate cancer.

POD-04.03

Chronic Diseases, Prostate Cancer Aggressiveness and Mortality after Radical Prostatectomy

Allard, Marc-André[1]; Caron, André[2]; Nguile Makao, Molière[2]; Lacombe, Louis[3]; Fradet, Yves[3]; Leger, Caroline[2]; Fradet, Vincent[3]
[1]Université Laval, Quebec, QC, Canada; [2]Centre de recherche du Centre Hospitalier Universitaire de Québec, Quebec, QC, Canada; [3]Centre Hospitalier Universitaire de Québec; Université Laval, Quebec, QC, Canada

Introduction and Objectives: Early clinical,epidemiological and experimental studies are linking cancer to various chronic medical conditions. Little is known of the association between prostate cancer (PCa) and chronic diseases and their effects on mortality after radical prostatectomy (RP). Our objective was to evaluate the impact of chronic diseases on mortality from PCa (DOD) versus from other causes (DOOC) after RP.

Methods: We did a retrospective cohort study of all RP patients at our centre who are included in our database with at least 5 years of follow-up (2734 patients, RP date 1987-2007) with available comorbidity information at surgery. Charlson comorbidity score (CCS) was calculated. To validate mortality data,we matched our institutional database to the Institut de la Statistique du Québec (June 2011). Cause of mortality was determined from chart review and death certificates. We examined the associations between the CCS and disease aggressiveness parameters at RP. We conducted univariate and multivariate survival analyses assessing time to DOD vs. DOOC.

Results: Mean patient age was 62.9.Mean follow-up was 8.8 years. Pathologic tumour Gleason grade was ≥8 and =7 in 19% and 41%. Stage was T4 in 2% and T3 in 38% of cases.CCS was of 0, 1, 2 and ≥3 in 1757, 598, 262 and 117 patients. CCS was positively associated with PCa aggressiveness at prostatectomy, both in terms of tumour grade (M-H chi-square p=0.0006) and stage (p=0.0015). At multivariate Cox regression, we observed an increased risk of DOD with increasing tumour stage (p=0.0001) and grade (p<0.0001) but also with increasing Charlson score (p=0.0029) in which is reproduced in a Kaplan-Meier model (p=0.0052). In contrast, we observed an increased risk of DOOC with increasing CCS (p<0.0001) but not with PCa grade or stage (p=0.9).

Conclusions: The CCS is a valid stratification tool for the risk of mortality from other causes in patients undergoing radical prostatectomy, validating previous findings. We observed a strong association between comorbidities and PCa aggressiveness and mortality, in particular DOD. This suggests a common link between chronic diseases and prostate cancer aggressiveness. Further research is justified to identify this link.

POD-04.04

Multicentre Assessment of Neoadjuvant Chemotherapy for Muscle-invasive Bladder Cancer

Youssef, David[1]; Zargar, Homayoun[2]; Espiritu, Patrick N.[3]; Fairey, Adrian[4]; Mertens, Laura[5]; Dinney, Colin P.[6]; Mir, Maria C.[2]; Krabbe, Laura-Maria[7]; Cookson, Michael S.[8]; Jacobsen, Niels-Erik[9]; Gandhi, Nilay[10]; Griffin, Joshua[11]; Montgomery, Jeffrey S.[12]; Vasdev, Nikhil[13]; Yu, Evan Y.[14]; Xylinas, Evanguelos[15]; Campain, Nicholas J.[16]; Kassouf, Wassim[17]; Dall'Era, Marc A.[18]; Seah, Jo-An[19]; Sridhar, Srikala[19]; Horenblas, Simon[5]; Aning, Jonathan[13]; Shariat, Shahrokh F.[15]; Wright, Jonathan L.[14]; Thorpe, Andrew C.[13]; Holzbeierlein, Jeff M.[11]; Bivalacqua, Trinity J.[10]; North, Scott[20]; Barocas, Daniel A.[21]; Lotan, Yair[7]; Stephenson, Andrew J.[2]; Shah, Jay B.[6]; van Rhijn, Bas W.[5]; Daneshmand, Siamak[4]; Spiess, Philippe E.[3]; Black, Peter[2]
[1]Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada; [2]Vancouver Prostate Centre, Vancouver, BC, Canada; [3]Department of Genitourinary Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, United States; [4]USC/Norris Comprehensive Cancer Center, Institute of Urology, University of Southern California, Los Angeles, CA, United States; [5]Department of Urology, The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands; [6]Department of Urology, MD Anderson Cancer Center, Houston, TX, United States; [7]Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX, United States; [8]Department of Urology, University of Oklahoma College of Medicine, Norman, OK, United States; [9]University of Alberta, Edmonton, AB, Canada; [10]Department of Urology, The James Buchanan Brady Urological Institute, The Johns Hopkins School of Medicine, Baltimore, MD, United States; [11]Department of Urology, University of Kansas Medical Center, Kansas City, KS, United States; [12]Department of Urology, University of Michigan Health System, Ann Arbor, MI, United States; [13]Department of Urology, Freeman Hospital, Newcastle Upon Tyne, United Kingdom; [14]Department of Urology, University of Washington School of Medicine, Fred Hutchinson Cancer Research Center, Seattle, WA, United States; [15]Department of Urology, Weill Cornell Medical College, Presbyterian Hospital, New York, NY, United States; [16]Department of Surgery, Exeter Surgical Health Services Research Unit, Royal Devon and Exeter NHS Trust, Exeter, United Kingdom; [17]Department of Surgery, Division of Urology, McGill University Health Centre, Montreal, QC, Canada; [18]Department of Urology, University of California at Davis, Davis Medical Center, Sacramento, CA, United States; [19]Princess Margaret Hospital, Toronto, ON, Canada; [20]Cross Cancer Institute, Edmonton, AB, Canada; [21]Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN, United States

Introduction: The efficacy of neoadjuvant chemotherapy (NAC) for muscle invasive bladder cancer (MIBC) was established with MVAC (methotrexate, vinblastine, doxorubicin, cisplatin), with complete response rates up to 38%. Due to comparable efficacy with better tolerability in patients with metastatic disease, GC (gemcitabine, cisplatin) has become the most commonly used NAC. We aimed to assess "real world" pathological rates to NAC with different regimens in a multicentre cohort.

Methods: Data was collected retrospectively at 16 international centres on sequential patients with MIBC (clinical T2-T4a, N0-3, M0) who received NAC, consisting of ≥3 cycles, followed by radical cystectomy, between 2000-2013. Patients with histology other than mixed urothelial carcinoma with squamous or glandular differentiation were excluded. The primary outcome was pathologic stage at cystectomy. Univariate and multivariable analyses were used to determine factors predictive of pT0N0 stage.

Results: Data on 1449 patients were collected, of whom 954 (65.8%) had a clinical node stage N0 (cN0) and 277 (19.1%) had cN1-3 (remaining 15.0% cNx). The majority received GC (n=816; 56%), followed by MVAC (n=405; 28%), and gemcitabine/carboplatin or other regimens (n=217; 15%). In the cN0 group, 22.3% (n=212) had pT0N0 on final histology and 41.1% (n=391) had pT1N0 or lower stage. The rate of pT0N0 for cN0 patients receiving GC was 22.2% compared to 25.9% for MVAC (p=0.2). On multivariable analysis for all patients (cN0 and cN+) MVAC was a statistically significant factor associated with pT0 (p=0.04) but not ≤pT1 disease (p=0.17). For patients with cN0, there was no difference between MVAC and GC in pT0N0 on multivariable analysis (OR 1.19 (95% CI 0.868-1.632); p=0.28).

Conclusions: NAC response rates in an international cohort are lower than those reported in prospective randomized trial. The use of MVAC compared to GC was predictive of a higher likelihood of patients achieving pT0N0 after NAC.

POD-04.05

Results of a Randomized Control Trial Assessing Enhanced Recovery after Surgery in Patients Undergoing Radical Cystectomy for Bladder Cancer

Aning, Jonathan; Black, Peter; Ischia, Joseph; Zargar, Homayoun; So, Alan
Vancouver Prostate Centre, Vancouver, BC, Canada

Objectives: Enhanced recovery after surgery (ERAS) is a comprehensive and multimodal perioperative care pathway designed to achieve early recovery for patients undergoing major surgery. Although considered standard of care for many different surgeries, there is limited experience of ERAS in radical cystectomy. We completed a randomized controlled trial in patients undergoing radical cystectomy for bladder cancer comparing an ERAS protocol compared to a more conservative standard of care treatment regimen.

Methods: 30 patients with bladder cancer undergoing radical cystectomy were prospectively randomised at decision to undergo surgery to an ERAS protocol (n=15) with early enteral feeding as its key component (starting day 1) or conservative management (CM) (n=15) to feed patients (time

of flatulence or bowel movement). Primary endpoint included length of stay and quality of life assessment on post-op days 3, 7, and 14 and secondary endpoints included complication rates in the first 30 days and time to flatulence.

Results: The mean length of stay was significantly shorter in the ERAS group (mean= 6.5 days) compared to the CM group (mean = 13.5 days, p=0.05). Median length of stay in the ERAS group was 6.5 days (range: 6-9 days) and was 7.5 days (range: 5-69 days) in the CM group. No differences in mean time to flatulence between ERAS vs. CM was found (4.1 days vs. 3.7 days respectively, p=0.1). More patients in the CM group received TPN but no differences were found in 30 day readmission rates. Assessment of QoL questionnaire is ongoing and will be presented.

Conclusions: Although patients undergoing radical cystectomy in the ERAS group had shorter hospital stay, no differences were found in time to flatulence or 30-day readmission rates. Our results show that ERAS with early feeding is safe and well-tolerated by patients undergoing radical cystectomy. Enhanced recovery protocols will continue to evolve and should be further studied in patients undergoing radical cystectomy.

POD-04.06

Outcomes of Progression on Surveillance for Clinical Stage I Non-seminoma Germ Cell Tumours

Nayan, Madhur[1]; Jewett, Michael[2]; Anson-Cartwright, Lynn[2]; Bedard, Philippe[2]; Moore, Malcolm[2]; Chung, Peter[2]; Warde, Padraig[2]; Sweet, Joan[2]; O'Malley, Martin[2]; Hamilton, Robert[2]

[1]University of Toronto, Toronto, ON, Canada; [2]University Health Network, Princess Margaret Hospital, Toronto, ON, Canada

Introduction and Objectives: Active surveillance (AS) as the initial approach for non-seminoma germ cell tumours (NSGCT) is universal for clinical stage (CS) 1A and adopted by most centres for CS1B. Patients progressing on AS have been typically treated with chemotherapy, but there is no consensus. We describe patterns and mode of detection of relapse and treatment of relapses in our NSGCT AS cohort.

Methods: From December 1980 to August 2011, 466 CSI NSGCT patients were managed with AS and 133 (28%) had disease progression while on AS. Logistic regression was used to explore factors associated with further treatment after RPLND.

Results: Median time to progression was 7.3 months and was detected by routine imaging (47%), routine serum tumour markers (37%), or both (12%). Progression occurred in the retroperitoneum alone (65%) most commonly. Following progression, first-line treatment was chemotherapy for 71 (53%), retroperitoneal lymphadenectomy (RPLND) for 51 (38%), and 11 (8.3%) underwent other therapy. Choice of first-line treatment was based on site and extent of relapse. In 78 (59%), only one modality of treatment was required: chemotherapy only in 40/71 (56%); RPLND only in 36/51 (71%). Elevated tumour markers pre-RPLND was the only factor associated with the requiring further therapy (OR 6.09; p=0.027). When RPLND was performed without elevated tumour markers, 83% required no further treatment. Overall, a second relapse occurred in 25/133 (19%) patients. With a median follow-up of 7.9 years, there were 5 deaths (3.8% of AS progressors) from testis cancer.

Conclusions: Routine imaging and serum tumour markers identify most progressors on surveillance for CSI NSGCTs, with the majority of patients progressing in the retroperitoneum within the first year. Of those patients that progress, most will achieve complete response with single modality treatment. In particular, RPLND can be utilized as monotherapy in select cases.