258 INVITED

Does Surgery Improve Outcome?

Abstract not received

Scientific Symposium (Mon, 26 Sep, 09:00−11:00) From New Targets to New Drugs in Prostate Cancer

259 INVITED

Bone Targeting

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The skeleton is the primary site of metastases in patients with advanced prostate cancer, and virtually all patients who die from prostate cancer have bone metastases.
Under normal conditions, bone undergoes continuous remodelling in a tightly coordinated and balanced process of bone resorption (mediated by osteoclasts) and bone formation (mediated by osteoblasts). In bone metastases, modifications in the molecular talk between osteoblasts and osteoclasts are induced by cancer cells, resulting in a "vicious cycle" (Guise et al, 2000). Bisphosphonates are potent inhibitors of osteoclastic bone resorption and until recently, zoledronic acid was the only bisphophonate to demonstrate in a randomized trial a reduction in the incidence of skeletal-related events (SRE) (Saad et al, 2004). Besides bisphophonates, the main and currently most advanced attempts to target osteoclast activation by cancer cells include denosumab, a fully human monoclonal antibody directed to RANK-L, which was shown to reduce uNTx levels significantly better than zoledronic acid does in patients with bone metastases and elevated levels while on IV bisphosphonate (Fizazi et al, 2009). Denosumab was demonstrated to be superior to zoledronic acid in preventing or delaying SRE in patients with bone metastases from castration-resistant prostate cancer (CRPC) in a large phase III trial (Fizazi et al., 2011). Denosumab was also recently reported to delay the onset of bone metastases in patients with non-metastatic CRPC in another phase III trial (Smith et al, 2011). Activation of the endothelin A (ET_A) receptor by endothelin-1 mediates a signalling cascade, which promotes tumour cell growth and survival, angiogenesis, invasion and metastasis, and inhibition of apoptosis. Zibotentan (ZD4054) is an oral, specific ET_A receptor antagonist with promising results in a randomised phase II trial (James et al, 2008). A large phase III programme is ongoing (ENTHUSE) to evaluate zibotentan in CRPC in various settings: in prevention of bone metastases, before chemotherapy, and in combination with docetaxel.
Dasatinib, a Src inhibitor was also demonstrated to result in decreased uNTx levels in patients with bone metastases (Yu EY et al, 2011) and is currently assessed in a phase III study in combination with docetaxel. XL-184 is a new MET- and VEGF-R targeting agent with preliminary very promising clinical activity in men with established bone metastases from prostate cancer.
Finally, phase II data support the use of a bone-targeting strategy combining chemotherapy and radiopharmaceuticals like samarium-153 (Fizazi et al, 2009) or strontium-89 (Tu et al, 2001). Results from a phase III trial assessing Radium-223, an alpha-emitter with high affinity to the bone, are awaited soon in men with bone metastases from CRPC.

260 INVITED

Androgen Receptor

Abstract not received

261 INVITED

New Chemotherapy Agents

Abstract not received

262 INVITED

From New Targets to New Drugs in Prostate Cancer − Other Targets

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Systemic therapy for castration-resistant prostate cancer (CRPC) has advanced significantly fueled by the increased understanding of the molecular mechanisms underlying progression. Beyond the successes in the development of more potent inhibitors of androgen receptor signaling, bone metastases targeting and new cytotoxic chemotherapy, there are a number of promising agents in clinical testing that are directed against a diverse array of additional targets. In the past, targeting angiogenesis pathways have had variable results, although more recently interesting outcomes have been reported from a randomized phase 2 trial with cabozantinib, a multi-receptor tyrosine kinase inhibitor including VEGFR2 and MET, demonstrating improvements in disease imaging and symptoms. Tasquinimod is a quinoline-3-carboxamide derivative with anti-angiogenic activity that has also demonstrated activity in a randomized phase 2 study with a delay in time to progression and a phase 3 trial has been initiated in chemotherapy naive patients. Key signal transduction regulators that have been identified as attractive targets for CRPC include the Src family kinases which have been implicated in bone metastases progression; and PI3-kinase and Akt in part owing to the frequency of PTEN alterations in CRPC. Dasatinib is a tyrosine kinase inhibitor with activity against Src and a phase 3 study in combination with docetaxel has recently completed accrual. Agents directed against chaperone proteins like heat shock proteins and clusterin are also in clinical development. Custirsen is a second generation antisense inhibitor of clusterin that when combined with docetaxel was associated with an improved overall survival in a randomized phase 2 study and phase 3 studies of this combination are ongoing. Several other agents in combination with docetaxel are in phase 3 testing and include aflibercept, lenalidomide, and the endothelin receptor antagonists atrasentan and zibotentan. Immunotherapy approaches to CRPC currently in phase 3 testing include ipilimumab, a monoclonal antibody against CTLA-4, and PROSTVAC, a poxvirus based therapeutic vaccine with PSA as the target antigen. A common drug development challenge for many of these agents has been that PSA decline as an endpoint has not corresponded with observed clinical benefits. This has been overcome in part by efforts to define progression independent of PSA effects and identification of novel biomarkers like circulating tumour cells.

Scientific Symposium (Mon, 26 Sep, 09:00−11:00) Survivorship and Life Style Changes After Cancer (Diagnosis)

263 INVITED

Breast Cancer and Return to Work

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Breast cancer is the most common cancer diagnosis in women, many of whom are of working ages, and the five-year survival rate is approaching 90 per cent. Accordingly, aspects of working life and sickness absence are of increasing importance in health care of these women. Nevertheless, there is little knowledge both about factors that promote (return to) work as well as about the meaning work has for these women. Moreover, even more basic information about occurrence and duration of sick leave after breast cancer diagnoses and surgery is lacking, although such aspects probably have long-term impact on the health and their quality of life. Knowledge is also lacking about sick leave already before the breast cancer diagnosis and how many that get disability pension due to breast cancer.
Previously, the main focus of psychosocial care and research on breast cancer has been crisis management. Now, a strong focus on return to everyday life, including work, need to be added. For research, this involves specific challenges regarding study designs and type of measures regarding for instance sick leave, activity, work, work incapacity, and return to work. Regarding the care of these women, other aspects are important; such as how care can be arranged to facilitate work, both regarding content and logistics. The need for sickness absence is associated with several aspects, such as severity of cancer, co morbidity, type of treatment, age, educational level, and type of work demands of the woman. Can sickness absence, of different durations and grades (full- or part time), lead to negative side effects for e.g. life style, mental disorders, occupational career, life situation, social contacts, or work capacity? How can we prevent such negative effects? What are the possible negative effects of sickness presence?
In this presentation these aspects will be discussed using data from systematic literature reviews and cohort studies.

264 INVITED

Addressing Consequences of Treatment − the Role of Rehabilitation

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It is an incredibly exciting and yet challenging time to be an Allied Health Professional (AHP) working in the field of cancer rehabilitation. The improved survival for many cancers and the increasing complexity of cancer treatment have resulted in a growing recognition and demand for

comprehensive rehabilitation services. However, despite significant drivers in the UK, such as the NICE Guidance in Supportive and Palliative Care (NICE 2004) and the Cancer Reform Strategy (DOH 2007), rehabilitation is often still considered the 'icing on the cake' and is not properly planned or implemented.
This presentation will focus on the rehabilitation needs of breast cancer patients, with a particular focus on physiotherapy interventions. It is well known that patients can experience a wide range of physical problems following treatment; many of which can impact on quality of life and function. Some of these problems are due to surgical interventions e.g axillary web syndrome (post axillary dissection) and myofascial restrictions in the chest wall (post mastectomy). Others, such as cancer-related fatigue are consequences of chemotherapy and/or radiotherapy. Physiotherapy has an important role in the evidence-based management of problems such as upper limb dysfunction and physical deconditioning. These physical sequelae will be discussed in some detail, along with guidance for other healthcare professionals on how to identify and manage problems and when to refer on. Particular attention will be paid to Axillary web syndrome or 'cording', and some preliminary research involving ultrasonography will also be discussed.
The National Cancer Action Team have recently produced evidence-based rehabilitation pathways and these provide a 'gold-standard' comparator against which services can be measured. The challenge remains to deliver this high quality care wherever and whenever it is required. Improving the commissioning of rehabilitation services is a national priority and AHPs must work closely with commissioners to demonstrate the value of their interventions and the vital role they play in improving patient care.

265 INVITED

Cancer as a Teachable Moment

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A "teachable moment" is often used to describe naturally occurring life transitions or health events thought to motivate individuals to adopt risk reducing health behaviours. When the timing is right the ability to learn is possible.
Cancer is still one of the most traumatic experiences that people have to face today. It can provoke a range of emotions including severe distress, feelings of anxiety, depression and uncertainty. For many it can trigger an existential crisis, challenging people's perception of themselves, their existence in the world and their sense of purpose and meaning in life. This impact goes beyond the person with cancer, to affect families, friends and carers.
Interestingly the Chinese character for 'crisis' combines the characters for danger and opportunity, a diagnosis of cancer and its subsequent impact on peoples lives certainly offers both. People who have successfully passed through the crisis phase of cancer have faced danger and decisions but also have the opportunity for change and growth. Changes catalyzed by a confrontation with death are described by Yalom (2008) as an "Awakening Experience", when you are faced with your own mortality and existence one is more anxious and 'primed to make significant changes', and prompted to rexamine who and where you are in the world, beginning to build an authentic life of engagement, connectivity, meaning and self-fulfillment. There are many points throughout the cancer journey from diagnosis to death which are opportunities for an awakening experience.
Since 1996 Maggie's (cancer charity) has been pioneering a new approach to cancer support in the UK utilising these moments of awakening as teaching opportunities. From our current ten centres (UK) and online centre we provide informational, practical, emotional and psychological support to all those people affected by cancer including family and friends, to enable them to manage the process of diagnosis as effectively as possible, experiencing a good quality of life throughout treatment and beyond. Maggie's centres are non institutionalised homely, uplifting buildings where people are welcomed by a team of qualified healthcare professionals including Cancer Support Specialists, Psychologists and Welfare Benefit Advisors. People can drop-in no appointment is necessary and an evidence based programme of support is available including individual or group support. The programme of support includes professionally facilitated support groups, psycho-educational courses/workshops such as nutrition stress management, supporting someone with cancer, and moving forward after cancer. It is a space where people can just "be" or meet others in a similar situation around our kitchen table.
Maggie's focus on psychological support and clear information links into the UK Governments Cancer Reform Strategy (2007) which points to the need to support and empower people through and beyond their cancer journey and recognises Maggie's as a leader in this area.

Scientific Symposium (Mon, 26 Sep, 09:00−11:00)
Tailoring Personalised Medicine for The Future

266 INVITED

Biomarkers in Early Phase Therapy Trials

A. Adjei[1]. [1]*Roswell Park Cancer Institute, Department of Medicine, Buffalo, USA*

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of pharmacologic responses to therapeutic intervention. With the advent of anticancer agents targeting specific proteins in cancer cells, it has become important to determine if a new drug is interacting with and modulating its target. In first-in-human studies, biomarkers are utilized as pharmacodynamic markers, which confirm that the drug is hitting its target. The most successful use of biomarkers have been as predictive markers, predicting tumour response if the biomarkers are present. Such biomarkers include EGFR mutations, EML4-ALK translocation, B-raf mutations, HER-2/neu expression and the oldest predictive marker of all, estrogen and progesterone receptors and response to tamoxifen and aromatase inhibitors. Prognostic biomarkers identify a patient population with a good (or bad) outcome (K-ras mutation in CRC with anti-EGFR antibodies). Unfortunately, a lot of prognostic markers are also predictive, creating complexities in study designs for validating biomarkers. Such examples will be highlighted. Finally, the challenges in using PD biomarkers incorrectly in predicting drug response in early stage trials will be highlighted. Also highlighted will be the pitfalls in using PD markers to guide dose selection, the so-called "optimal biologic dose".

267 INVITED

Personalised Therapy in Breast Cancer

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Background: The inability of breast cancer (BC) cells deficient in homologous recombination to repair DNA double strand breaks (DSBs), such as *BRCA1/-2*-mutated cells, offers a target for DNA crosslinking agents, e.g. bifunctional alkylating agents or platinum compounds. *In vitro* screens and studies in genetically engineered mouse models for *BRCA*-mutated breast cancer have shown that these tumours can only be eradicated with high doses of DSB-inducing agents.
Our group previously employed array Comparative Genomic Hybridization (aCGH) to assess the genomic patterns of human breast cancers with loss of BRCA1- or BRCA2. We hypothesized that these patterns might also be present in some sporadic BCs and might predict for improved outcome after treatment with high doses of DNA crosslinking agents.
Material & Methods: BRCA-like^{CGH} status, defined as positive when the previously published BRCA1-like^{CGH} and/or BRCA2-like^{CGH} pattern was present, was assessed in 249 stage-III, HER2-negative BC patients, who had participated in a randomized controlled trial studying adjuvant high-dose (HD) cyclophosphamide-thiotepa-carboplatin (CTC) versus conventional 5-fluorouracil-epirubicin-cyclophosphamide ($FE_{90}C$) chemotherapy. We evaluated whether the effect on recurrence-free and overall survival (RFS, OS) of HD-CTC compared to conventional $FE_{90}C$ differed by BRCA-like^{CGH} status, stratified for 4−9 versus 10+ involved lymph nodes and triple negative status, and adjusted for tumour size and grade.
Results: 81 patients (81/249, 32%) appeared to have BRCA-like^{CGH} tumours and had a significant benefit of HD-CTC compared to conventional $FE_{90}C$ regarding OS (adjusted HR 0.19, 95% CI: 0.08–0.48), while HD-CTC was not superior among patients with a Non-BRCA-like^{CGH} tumour (adjusted HR 0.90, 95% CI: 0.53–1.54). The difference was statistically significant (p-interaction: 0.004). Similar results were found for RFS. Sensitivity analyses showed that the aCGH test was robust and not dependent on small changes in tumour percentage or thresholds. Half of all BRCA-like tumours were ER-positive; 14% of BRCA1-like and 69% of BRCA2-like tumours. Twelve cases were both BRCA1- and BRCA2-like.
Conclusions: aCGH genomic patterns identify both ER-positive and triple negative BC patients who derive a marked survival benefit from high-dose DNA crosslinking chemotherapy.

268 INVITED

Personalised Therapy in Lung Cancer

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A proposed model for DNA damage response to irradiation involves the formation of a BRCA1 complex. In DNA damage response, ATM and ATR phosphorylate H2AX on Ser-139, which serves to recruit the MDC1 protein