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

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Bone Targeting

K. Fizazi[1], C. Massard[1], Y. Loriot[1]. [1]*Institut Gustave Roussy, Department of Cancer Medicine, Villejuif, France*

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

K.N. Chi[1]. [1]*BC Cancer Agency − Vancouver Cancer Centre, Medical Oncology, Vancouver, Canada*

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

K. Alexanderson[1]. [1]*Karolinska Institutet, Clinical Neuroscience, Stockholm, Sweden*

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.

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Addressing Consequences of Treatment − the Role of Rehabilitation

K. Robb[1]. [1]*Barts Hospital, Physiotherapy Department, London, United Kingdom*

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