145 INVITED

Novel Targets and New Treatment

Abstract not received

146 INVITED

Cancer Survivorship

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During the last three decades testicular cancer (TC) has served as a model for a curable solid tumour. Increasing prevalence of TC and survival rates of 95% contribute to a growing community of Testicular Cancer Survivors (TCSs) [1].
Cure, however, usually comes at a cost in form of long-term toxicities ranging from the rare but life-threatening induction of second cancers to the more common complaints like paresthesias, tinnitus or hearing impairment [2].
Typically, life expectancy after treatment amounts to several decades, permitting assessment of quality of life in the long-term. Treatment modalities ranging from orchiectomy only to chemotherapy, advanced surgery, radiotherapy, sometimes given in combinations, allow attribution of toxicities to specific treatments. Further, realization of the aim to reduce toxicities while maintaining survival requires evaluation of long-term complications.
In this presentation we intend to give an overview about the following long-term complications: cardiovascular disease, neurotoxicity, pulmonary toxicity, hypogonadism, decreased fertility, and psychosocial problems. Quality of Life, however, is, despite the many unintended side effects of treatment, similar to the normal population [3].
We believe that survivorship studies are particularly worthwhile among TCSs and hope that the presented results provide relevant information also to other cancer patients and their oncologists [4].

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Special Session (Sun, 25 Sep, 13:15−14:15)
New Insights in Molecular Targeting in Radiotherapy

147 INVITED

EGFR-Inhibition − Pre-clinical and Clinical Update

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The Epidermal growth factor receptor (EGFR) is overexpressed in many human tumours. Its expression correlates with a poor prognosis in many types of cancer. The anti-epidermal growth factor receptor (EGFR) antibody Cetuximab has been the first molecular targeted agent that was approved some years ago for simultaneous use to curatively intended radiotherapy in head and neck cancer patients. In an unselected group of patients, this combined treatment improves local tumour control and survival compared to radiotherapy alone. However, the cure rates are not higher than observed after standard radiochemotherapy and there are recent reports on a relatively high acute toxicity of Cetuximab when applied during radiotherapy. Moreover, early clinical trials on combined radiochemotherapy and Cetuximab in rectal cancer patients show low pathological complete response rates compared to historical controls.
Looking at tyrosine kinase inhibitors, palliative potential has been shown e.g. in non-small-cell lung cancer. Here, biomarkers have been established that correlate with response and survival. Using such biomarkers, in selected patients with specific EGFR mutations, superiority of the TK-inhibitor gefitinib over chemotherapy has been shown in a randomised trial. Also for radiotherapy and Cetuximab, the intertumoral heterogeneity of response is large, as observed in preclinical experiments and in clinical studies. Thus, it can be expected that the development of biomarkers predicting local tumour control for this combined treatment, would help to more efficiently use this treatment option and thereby increase local tumour control and survival in subgroups of patients. First clinical and preclinical results are available suggesting an importance of EGFR protein or EGFR gene expression for treatment outcome. Further validation studies are warranted to finally establish these or other biomarkers as clinical predictors.
An overview will be given on current clinical data in correlation with mechanistic preclinical investigations.
Supported by Deutsche Forschungsgemeinschaft (DFG-PAK190)

148 INVITED

New Molecular Targets in the Tumour

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Combination of chemotherapy and radiotherapy is a mainstay in the management of patients with locally advanced tumours. Our increased knowledge of cancer at the molecular level has transformed our understanding of tumour radiation response. Several agents designed to target specifically these molecular processes can increase tumour response to ionising radiation *in vitro* or *in vivo*. Many of these agents are in the process of clinical evaluation with radiotherapy. The challenging concept of tumour addiction and the increasing pharmacological tools available to reverse these signals may represent a novel step in the concept of tumour radiosensitization. We have developed a strategy for the treatment of HPV related tumours: the use of antiviral agents to modulate the radiosensitivity. However, in lung tumours, some data suggest that inhibition of cancer 'addiction' pathways may not always necessarily translate in better response to IR into the clinic.
These data justify the importance of evaluating new agents in combination with irradiation with an appropriate methodology at the preclinical stage in order to avoid unnecessary exposure of patients to potentially ineffective or detrimental combinations.
This preclinical evaluation needs to 1) evaluate the toxicity profile, 2) compare the antitumour efficacy observed with other radiosensitizing agents, 3) Characterize optimal tumour biological characteristics and 4) Define the sequence adapted to the optimal antitumour effect.
An important aspect is also to take into account the mechanisms of action of ionizing radiation such as DNA damage and cell cycle check-point induction during repeated DNA daily fractions. These aspects can be used to increase tumour response to irradiation. In particular, induction of mitotic catastrophe, one key mechanism of tumour cell death after irradiation can be increased by the use of agents that override the radiation induced G2/M arrest such as CHK1/2 and aurora inhibitors. Of interest, this latter approach exploits differences in radiation response of p53 deficient versus p53 wild type cells which could eventually provide exploitable differential effect in the clinic.
In contrast to the preclinical findings, clinical results from clinical trials combining radiotherapy to targeted therapies such as anti EGFR or anti VEGF has been sometimes associated to an increase in toxicities underscoring the need for appropriate models of tumour versus normal tissue response assessment in vivo. The development of more relevant preclinical models of drugs-radiotherapy toxicities will be illustrated through the evaluation of the impact of new strategies on the response of non-tumour tissues. Moreover, one of the major issues is to improve the relevance of preclinical models which will have to integrate novel concepts such as tumour microenvironment, immune response in order to maximise the changes of success for subsequent clinical transfer.

149 INVITED

Molecular Pathways in Radiation Fibrosis

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During the past 20 years, the signals involved in the development and maintenance of radiation fibrosis have been extensively studied. Today, several fibrogenic pathway have been identified and offer a range of therapeutic targets that have been validated in experimental models but need to be tested in clinical trials.
Among these factors, transforming growth factor beta 1 (TGFb1) is described as the primary inductor of the fibrogenic process. Stored in a latent form (LTGFb1), TGFb1 is is activated by the actions of proteases (plasmin and thrombin) and reactive oxygen species (ionising radiation). It

binds to membrane receptors (types I and II serine/threonine kinases) that signal via the Smad pathway. Smads are signalling molecules, acting as transcription factors for genes coding for procollagens and other matrix compounds, and fibrogenic growth factors. Alternative signalling routes from the TGFb1 receptor (TGFb1R) complex to the nucleus bypass cytoplasmic Smad proteins, using the so-called p38, JNK, ras/ERK MAP kinase and Rho/rho kinase (ROCK) pathways. Anti-TGF-b1 strategies including soluble RII have shown efficacy to prevent and halt radiation-induced fibrogenic process and recently Pirfenidone has shown some effectiveness in halting diabetic nephropathy and IPF in humans. No trial is scheduled on radiation fibrosis, however due to the pleiotropic role of TGF-b1 in tissue homeostasis serious side-effects can be anticipated.
TGFb1 is not the only fibrogenic cytokine, the products of Thy-2 lymphocytes can be mentioned including IL-4 and IL-13. Amongst the growth factors bFGF, PDGF, IGF; and several chemokines such as ET-1 and CTGF form a longer list of potent fibrogenic factors acting alone or in conjunction with TGFb1.
PDGF family mainly target mesenchymal cells. Their physiological and fibrogenic actions are achieved by homodimerisation of the growth factors (creating PDGF-AA, PDGF-BB etc dimers) that bind to specific plasma membrane receptors (PDGFR-a and PDGFR-betc). PDGFR-a is transactivated by TGF-b1 and is especially associated with fibrosis. PDGF signals through major transduction pathways including PI3K, Ras/MAPK and PLCg to stimulate myofibroblast proliferation and extracellular matrix synthesis. Targeting PDGF pathway using Glivec prevented radiation-induced pulmonary fibrogenesis. Clinical trials are ongoing in systemic sclerosis, nephropathy and IPF but no specific trial on radiation fibrosis is planed so far.
CTGF is a matricellular protein that promotes fibroblast proliferation and ECM production *via* a yet uncharacterized membrane receptor. CTGF inhibition using anti-CTGF monoclonal antibody and Pravastatin has shown very promising results in both preventing and reversing radiation fibrosis in experimental rodent model. Therefore the anti-fibrotic efficacy of Pravastatin is currently investigated in a phase II/III study at IGR.

Special Session (Sun, 25 Sep, 13:15−14:15)
Fertility Concerns

150 INVITED

Frozen Hope − Fertility Preservation for Women With Cancer

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Increasingly successful treatments for cancer and higher survival rates mean that considering future fertility is an important factor in the treatment of pre menopausal and nulliparous women and younger girls. The parallel scientific and clinical advances in reproductive technologies now present more options for the preservation of fertility at the time of treatment for cancer and assisted conception may be used for reduced fertility later in life.
The diagnosis of any type of cancer is usually devastating and confronting mortality and the other complex emotional, social and practical issues associated with preserving fertility is not easy for patients or practitioners when dealing simultaneously with all the other decisions.
Understandably the immediate emphasis is on the treatment for cancer and it may be difficult to think beyond to life later on. The psychological impact of the prospect of infertility may be mitigated by freezing embryos or oocytes (eggs). For women, the options for preserving their fertility depend on individual medical and social circumstances. Embryo freezing, first successful in 1983, is now a routine part of in vitro fertilisation cycles (IVF) but can only be used if the woman has a partner to create embryos or uses donated sperm. Cryopreservation of oocytes may be preferred by many women but it has proved more technically challenging. Although the first live birth from a cryopreserved oocyte was reported in 1986 the success rates remain low and it is much less widely available than embryo freezing. Research is ongoing into freezing ovarian tissue and this may be an option in the future. Most people would choose to have their own genetic children but using donated eggs may be considered by women who are infertile after the treatment for cancer if preservation of embryos or oocytes fails or are not chosen for medical or personal reasons. The window of opportunity for preserving embryos and oocytes is limited and a decision may have to be made about whether to delay starting treatment to take advantage of these options. However with the advances in fertility preservation and treatment, an integral part of cancer care should be discussing the implications for reproduction and counselling patients to help with their decisions. The legal and regulatory framework will also impact on what may be offered, for example embryo freezing is not allowed in some countries. Some cancer centres have established links with assisted conception units to provide fertility oncology services but this is not yet routine.

151 INVITED

Male Infertility and Cancer

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Many cancer treatments increase the risk male infertility, particularly those involving irradiation of the pelvis and/or systemic treatment with chemotherapy drugs. Hence, the opportunity to bank sperm, before cancer treatment begins, is invaluable for many males as 'fertility insurance'.
Sperm banking has been technically possible since the 1950's, but the organisation of sperm banking services as part of oncology care only became developed in the 1970's. In spite of this long history, their remains considerable evidence today that many males are often not given the opportunity to bank sperm (or when it is offered they do not accept it). Consequently, the ability of some men to father children post-treatment will be compromised if their fertility does not recover.
The prospects of sperm production recommencing following cancer treatment among men who bank sperm is quite good with only a third of men remaining azoospermic in the long-term. However, data on the probability of male cancer survivors achieving paternity spontaneously (i.e. without assisted conception) is less clear with some studies providing conflicting estimates of how likely fatherhood may be.
If necessary, frozen-thawed sperm, or freshly ejaculated sperm (if some natural fertility returns), may be used in a variety of assisted conception procedures including Intra-Cytoplasmic Sperm Injection (ICSI). Even in men who are azoospermic after cancer treatment, current data suggests that sufficient numbers of sperm can sometimes be obtained from testicular biopsy to make fertilisation of oocytes using ICSI possible.
The long-term health outcome of children born to cancer-survivors is thought to be very good, although there are few studies that have looked at this cohort specifically. However, singleton babies born through assisted conception (using frozen or fresh sperm) are healthy as their naturally conceived counterparts. There is increasing recognition that the major adverse outcomes are associated with multiple births.
Unfortunately, for pre-pubertal males who could not bank sperm, or in post-pubertal males who were too ill or where banking was not offered, there are no known therapies to stimulate sperm production if it does not return naturally at the end of treatment. In such cases, the use of donor sperm or adoption remains the only known methods to allow such men to establish families.

152 INVITED

Same Sex Couples Fertility Issues

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I have made a Pub Med database search to see if there are differences concerning fertility issues between same sex couples and heterosexual couples.
The review did not find any publications concerning same sex couples fertility issues.
There are no differences in how to preserve fertility in heterosexual- or same sex couples.
The differences concern the attention on homosexual realities and psychosocial needs.
It has been shown that providers not inquire about sexual orientation. Same sex couples were afraid to reveal their sexual orientation out of fear of stigmatization and homophobia.
It is of great importance that the ambiance in healthcare is open concerning sexual orientation and that health givers ask about sexual orientation to make same sex couples feel at ease and then dare to disclose their sexual orientation.

Special Session (Sun, 25 Sep, 13:15−14:15)
Esophageal Cancer − Ways to Improve Outcome

153 INVITED

How Radical Should Surgery Be?

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Esophagectomy for carcinoma can be viewed as being comprised of two components: resection of the esophagus and resection of the enveloping lymphatics. Controversy exists regarding how radical, or extensive these two components should be. Non-radical (standard) resection of the esophagus involves simple extirpation of the organ,