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Novel Targets and New Treatment

Abstract not received

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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].

References

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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.
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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.

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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