Vaccines can be considered as so called specific immunotherapy. This is the reason why the above mentioned toxicities are not seen. Vaccines strategies like dendritic cells loaded with tumorproteins/peptides/RNA, GMCSF manipulated tumorcells or heatshock proteins have been explored in mRCC and in an adjuvant setting after tumornephrectomy for localized RCC. Only grade 1 toxicities were seen in about 30% of the patients.
In conclusion the side-effective profile of immunotherapy and vaccines is dependent on nature and the specificity of the approach and should be handled accordingly.

258 INVITED

Adjusting therapy in the elderly patient with metastatic renal cell cancer (mRCC)

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We know that the average age at presentation of renal cancer is 62 years in both men and women. Given that the number of elderly people is rapidly rising and that cancer incidence increases with age, we must expect an escalating burden of renal cell cancer in the coming years. The treatment of metastatic renal cancer has changed completely over the recent years with the introduction of different targeted therapies which have demonstrated a benefit in terms of both overall and progression-free survival. However, these new drugs induce toxicities which complicate the management of elderly patients. We know that older cancer patients have comorbidities which may affect treatment tolerability, as well as patient general prognosis and quality of life. No specific trial has been conducted in this particular population; the main results available come from clinical trials including only a limited number of patients older than 65 years. The six randomized trials testing sofafenib, sunitinib, bevacizumab, temsirolimus or everolimus had no upper age limit for recruitment. However, the average age of patients entered in these trials was quite similar and younger (58−62 years) than in the general population. In addition, subgroup analyses to assess the relationship of age to treatment benefit have limitations and should be regarded as hypothesis-generating and not as definitive evidence. Obviously, all these treatments have demonstrated efficacy in the elderly and the results obtained seem to be in the same range as in younger patients. Although it appears difficult to analyse the side-effects induced in the elderly population, some well-known toxicities from targeted therapies may have a more significant impact in this subgroup: hypertension, cardiac impairment, thromboembolism, asthenia and digestive symptoms, especially diarrhoea. In addition, elderly patients use a variety of drugs for managing comorbidities and these drugs may interact with targeted therapies. For these reasons, patients with several comorbidities and treatments may require an oncogeriatric evaluation before making a treatment decision. Stricter management with more frequent consultations may also be useful to avoid severe adverse events as well as major impairment in their quality of life.

Scientific Symposium (Wed, 23 Sep, 14:45−16:45)
Targeting in radiotherapy

259 INVITED

Targeting the tumour stroma

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Background: The tumour stroma plays an essential role in malignant transformation, tumour progression and development of resistance to conventional radio- and chemotherapy. It consists of different cell types such as fibroblasts, immune and inflammatory cells and endothelial cells and the connective-tissue framework/extracellular matrix (ECM). Although histological distinguishable, the tumour stroma and the tumour cells are functionally inevitable linked. On top of e.g. tumour cell-specific gain-of-function mutations, these interactions further promote the survival, growth and spread of the tumour cells via production of growth factors, extracellular matrix remodeling and by provoking a tumour-friendly microenvironment. Owing to these various prosurvival effects, targeting strategies against the tumour stroma might be reasonable and clinically achievable in modern radiochemotherapy. One of these potent strategies is the inhibition of integrin cell adhesion molecules. Integrins facilitate interactions between the cells of the tumour stroma and ECM and between cells of the tumour stroma and tumour cells.
Material and Methods: Different tumour cell lines, particularly head and neck squamous cell carcinomas, have been investigated under conventional monolayer and three-dimensional growth conditions and in vivo with regard to radio- and chemoresistance. Moreover, the results of targeting approaches against integrins and associated molecules evaluated in additional preclinical models and clinical trials will be discussed.
Results: Inhibition of integrins on both tumour stroma and tumour cells shows promising results. Other approaches against integrin associated signaling molecules such as Focal adhesion kinase or Rho-GTPases or ECM remodelling matrix metalloproteinases further underscore the relevance of these signaling pathways for therapy resistance and tumour progression. The findings also highlight dramatic effects of radiochemotherapy and particularly molecular therapeutics on the tumour stroma, at which the exact benefits and consequences in terms of cancer cure remain to be clarified. For example, the optimal sequence of antiangiogenic compounds in combination with radiotherapy is currently unclear.
Conclusions: The tumour stroma and the tumour microenvironment are integral functional parts in tumourigenesis, tumour progression and resistance to radio- and chemotherapy. Besides specific targeting of molecules essential for tumour cell survival and proliferation, targeting strategies against the tumour stroma have shown to be promising, powerful adjuvants for conventional anticancer treatment. Nevertheless, further efforts are warranted to understand the underlying molecular mechanisms that drive tumour growth in dependence on the tumour stroma for the development of more efficient molecular therapeutics.

261 INVITED

Improving radiotherapy by targeting the bone marrow derived stroma

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Tumor blood vessels can derive from two sources: by angiogenesis, or the sprouting of endothelial cells from nearby blood vessels, and by vasculogenesis, which is produced by circulating cells. We have recently proposed that the radiation doses given in radiotherapy, which produce very high local cell killing in and immediately surrounding the tumor, will abrogate local angiogenesis and thereby forcing tumor regrowth to rely on vasculogenesis. This alternative pathway involves the recruitment of proangiogenic circulating cells many of which are derived from the bone marrow. To investigate this hypothesis, we used the subcutaneously implanted FaDu human head and neck tumor and an orthotopic brain tumor using human U251 GBM cells that were retrovirally transduced with the luciferase gene in order to monitor tumor growth in real-time.
To examine the influence of irradiation on the influx of bone marrow derived cells (BMDCs) into the tumors, we sacrificed tumor-bearing nude mice containing GFP-expressing bone marrow when the tumors grew back to their pre-irradiation size following either 8 or 15 Gy. We found that irradiation induced BMDC influx in a dose-dependent manner with most of this increase reflecting influx of CD11b+ myelomonocytes. We postulated that this influx of BMDCs was stimulated by increased tumor hypoxia and HIF-1 levels caused by radiation damage to the tumor vasculature. To determine HIF-1 activity in real-time in our brain implanted U251 GBM, we stably expressed the HIF-1 reporter construct 5HRE-luc in U251 cells and monitored luciferase activity in control and irradiated tumors. HIF-1 activity paralleled tumor growth in non-irradiated tumors but increased more rapidly than tumor growth starting at about two weeks following 15 Gy, indicating increase in HIF-1 levels parallel to the increase in tumor hypoxia that we observed at this time.
To test our hypothesis that the increased HIF-1 levels were responsible for the increased influx of CD11b+ cells into the tumors, we used the HIF-1 inhibitor NSC-134754. When this inhibitor was given daily for 2 weeks, starting immediately following irradiation, the increased tumor levels of CD11b+ monocytes observed after 15 Gy was abrogated. This treatment also prevented recurrence of the irradiated tumors following irradiation even when we ceased administration of the drug.
As a further test of our hypothesis we determined the effect of inhibiting the interaction of stromal derived factor-1 (SDF-1) with its receptor CXCR4 using the clinically approved drug AMD3100. It has been shown that BMDCs are retained in hypoxic normal tissues and in tumors by the hypoxia-dependent secretion of SDF-1, which binds to its receptor, CXCR4, on BMD monocytes thereby promoting angiogenesis. To prevent this interaction we infused tumor-bearing mice with AMD3100 starting immediately following irradiation. This had no significant effect on the growth of unirradiated tumors in the brain but completely inhibited the recurrence of the irradiated tumors following either a single dose of 15 Gy or the more clinically relevant scheme of 5 daily doses of 2 Gy.
We also showed that the recurrence of FaDu tumors locally irradiated with 20 Gy is prevented using a monoclonal neutralizing antibody against CD11b+ monocytes. This treatment does not increase the radiosensitivity of normal skin. In fact we observed a consistent protection of the skin when the irradiated mice were treated with the antibody starting 4 days after irradiation