comprises mainly advances in treatment planning - in particular in regard of individual target (re-)definition based on tumour response and in regard of individual dwell time optimisation for improvement of the dose distribution: Repetitive imaging is necessary and allows for identification of tumour regression and organ changes. MRI is currently considered as the gold standard for the assessment of local tumour extension in cervical cancer and is therefore the method of choice for IGABT, however, CT, PET-CT and ultrasound were also described as feasible for brachytherapy treatment planning. With MRI, the target concept (high risk clinical target volume - HR CTV, intermediate risk clinical target volume - IRTV) for IGABT after external beam radiotherapy and chemotherapy implies the residual macroscopic tumour (GTV at brachytherapy), the surrounding tumour regression area ("grey zones"), the complete remaining cervix and the tumour extension at diagnosis with different dose aims respectively. The optimal fractionalisation scheme still remains unclear, but it was shown that the local control rate of 95% is achieved by a 90 Gy @ 87 Gy (EQD2) is delivered to the HR CTV. To reach this dose aim, the implantation of interstitial needles in addition to the standard applicator system may be necessary - especially in locally advanced tumours with extensive residual parametrial involvement or with unfavourable topography. The use of supplementary interstitial needles allows to increase and further shape the treated volume in order to avoid low dose regions within the target volumes and/or high dose delivery to surrounding organs at risk. The reduction of unintended dose to the surrounding organs at risk by IGABT confers a significantly decrease in morbidity as shown in retrospective studies and recently in the prospective STIC trial. The D2cc appears to be a reliable predictor for typical severe rectal brachytherapy related side-effects such as bleeding caused by angiodestruction and fistula as well as a potential (but less stable) indicator for localized bladder toxicity. It could be demonstrated that a D2cc of 73 Gy (EQD2) for grade 1-4 side effects and 78 Gy (EQD2) for grade 2-4 side effects leads to a 10% probability for the respective rectal side effects. Dosimetric comparisons between standard treatment plans based on dose points and IGABT showed a clear superiority of IGABT. Retrospective mono-institutional clinical results in 156 patients showed a local control rate of 95% and 65 grade 3 and 4 gastrointestinal and urogenital side effects after 3 years. The preliminary results from the retrospective multi-centre study "RetroEMBRACE" with 11 participating centres seem to confirm these results with 89% local control rate after 5 years in 645 patients. The prospective multi-centre trial "STIC" demonstrated a reduction of treatment related side effects by IGABT by 50% compared to standard x-ray based brachytherapy. Further evidence on IGABT is expected from the prospective multicenter study "EMBRACE", which currently recruited about 800 patients.

SYMPOSIUM: THE POTENTIAL FOR RT AND TARGETED THERAPIES: FIRST GENERATION STUDIES

SP-0508 Introduction to radiotherapy and novel promising radiosensitisers (HDACi, CHKi, mTORi) E. Deutscher1, Y. Tao1, S. Rivera2, Gustave Roussy, Radiation Oncology, Villejuif, France

There is considerable interest in approaches that could improve the therapeutic window of radiotherapy. As our understanding of cancer biology has expanded, novel candidate strategies have emerged in order to counteract the mechanisms of tumour radiationresistance which may explain the therapeutic failures after radiotherapy. Drugs which target the G2/M checkpoint after irradiation, lead to an increase in mitotic death are candidates which may induce an increase in tumor cell kill while relatively sparing non tumor tissues. Drugs such as CHK1 inhibitors, preferentially induce an override of the cycle check-points after IR, based on the p53 status. HDAC inhibitors are drugs which have in common the ability to hyperacetylate both histone and non histone targets, resulting in avariety of effects on cancer cells, their microenvironment, and immune responses. Data suggest that HDAC inhibitors not only induce widespread histoneacetylation but also increase in reactive oxygen species and DNA damage. ROS account for the DNA damage observed with HDACi treatment. DNA damage can also be the result of changes in the DNA repair activity and chromatin remodeling factors. This approach is currently being tested at our institution.

mTOR is one the downstream effectors of thePI3K-AKT pathway which plays a role in angiogenesis and hypoxic metabolism. mTOR inhibitors are currently approved as stand alone treatments and the combination of mTOR inhibitors with ionizing radiation has been evaluated in the setting of early clinical trials.

The major challenges of these novel approaches is the assessment of their clinical usefulness. This implies not only to show increased tumor cell kill in preclinical assays, but also to define which tumour biological background is optimal for the biological effect, which are the appropriate schedules and intervals between drug administration and irradiation. Notwithstanding, a cornerstone is the impact of any novel approach on normal tissue response to irradiation and the consequences on the tumor versus normal tissue therapeutic ratio.

SP-0509 Radiotherapy and PARP inhibitors: pre-clinical rationale and clinical experience

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Poly(ADP-ribose)polymerase (PARP) is a DNA repair enzyme that facilitates repair of radiation induced DNA single strand breaks. It is well established that chemical inhibitors of PARP increase radiation sensitivity of tumour cells in vitro and enhance tumour growth delay in pre-clinical animal models of cancer. PARP inhibitors also have single agent activity against BRCA-deficient breast and ovarian cancers and a number of compounds have been tested in early phase clinical trials in this setting. Toxicity profiles are acceptable and many patients tolerate long-term treatment without significant adverse effects.

Mechanistic studies in vitro have shown that the radiopotentiation effects of PARP inhibitors are observed only in replicating cells, and there is also evidence to support enhanced sensitisation in DNA repair defective cells. Both observations indicate the potential for tumour specific enhancement of the cytotoxic effects of radiation and support the argument to combine PARP inhibitors with radiation therapy in the clinic.

Despite the clear rationale, progress has been slow and at the time of writing only three clinical trials combining PARP inhibitors with radiation have opened to recruitment. To some extent, this can be explained a lack of validated clinical trials designs for radiation/drug combinations. Equally important is the observation that PARP inhibitors exacerbate haematological toxicity when delivered in combination with chemotherapy drugs such as temozolomide or cisplatin. Since curative radiation therapy regimes often include concomitant chemotherapy agents, alternative approaches are required.

In this presentation I will summarise the relevant pre-clinical data, give an update on clinical experiences and consider new approaches by which PARP inhibitors and radiotherapy might be safely and effectively combined.

SP-0510 Targeting the MET oncogene to radiosensitize cancer stem cells

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Solid tumours such as glioblastoma contain a cell subset endowed with stem properties (cancer stem cells), which is required and sufficient to drive tumour onset and propagation, as well as it is responsible for resistance to conventional therapies, and tumour relapse. It has been shown that glioblastoma stem cells are radiosensitive, likely because they activate the DNA repair machinery more efficiently than the remaining non-stem cancer cells, which, conversely, may be destroyed by radiotherapy. We have recently shown that cancer stem cell radiosensitivity is associated with overexpression and activation of the MET oncogene, encoding the tyrosine kinase receptor for HGF, known to regulate cancer ‘invasive growth’. MET overexpression is reported in significant percentages of tumours of various origins, including 30% of glioblastomas, often in association with poor prognosis. We have shown that ionizing radiation, through activation of DNA repair mechanisms and transcription factor NF-kB, sustains MET overexpression and activity. In glioblastoma, MET signalling results in hyperactivation of the PI3-kinase/AKT pathway, protection against radiation-induced apoptosis, and positive selection of the cancer stem cell subpopulation. Conversely, we have shown that targeting MET inhibition, by small-molecule kinase inhibitors or monoclonal antibodies, may radiosensitize cells in vitro and in vivo. Therefore, in glioblastoma and, possibly, other tumours, combination of MET inhibitors with radiotherapy offers a promising strategy to destroy cancer stem cells, and prevent tumour relapse.