2015 POSTER DISCUSSION

Pharmacological inhibitors of heat shock protein 90 can overcome radioresistance of tumor vasculature

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Background: Progression of solid tumors and their resistance to therapy strongly depend on the tumor vasculature delivering oxygen, nutrients and growth factors. Therefore, besides invasive tumor cells, the tumor vasculature cells are also a significant target for chemo- and radiotherapy. The aim of the present work was to study how 17-N-allilamino-17-demethoxygeldanamycin (17AAG) and 17-(dimethylaminoethylamino)-17-demethoxygeldanamycin (17DMAG), known as anticancer agents inhibiting heat shock protein 90 (HSP90), modifies responses of human vascular endothelial cells (EC) to growth factors and gamma-photon irradiation.
Material and Methods: EC cultured from human umbilical veins were exposed to vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) or/and gamma-irradiation (3−6 Gy) while some EC samples were pretreated with 17AAG or 17 DMAG (10–500 nM). The postirradiation cell death/survival and morphogenesis were assessed in TUNEL, annexin V-staining, clonogenic and tube formation assays. The drug-affected phosphorylation and expression of certain signaling- and apoptosis-related proteins were explored by Western blotting. Transient transfection with plasmids expressing dominant negative or constitutively active mutant Akt constructs was used to manipulate the Akt activation/expression levels in the EC cultures.
Results: It was found that nanomolar concentrations of 17AAG or 17DMAG inhibit the chaperone function of HSP90 in EC. Importantly, pretreatments with 17AAG or 17DMAG repressed a capability of the growth factor-stimulated EC to form capillary-like tubular structures (tubes) in Matrigel. Moreover, both the drugs were able to radiosensitize EC and fully abolish the radioprotection conferred by VEGF and bFGF. As it appears from the transfection experiments, these effects can be due to the drug-induced prevention of HSP90-dependent phosphorylation (activation) of Akt that resulted in blockade of the PI3K/Akt pathway; the latter is known to contribute to proliferation and radioresistance of vascular EC.
Conclusions: Clinically achievable (nanomolar) concentrations of 17AAG or 17DMAG can abrogate both the high radioresistance intrinsic to human vascular EC and the angiogenic and radioprotective action of tumor-derived growth factors such as VEGF and bFGF. This finding gives additional rationale for combining anticancer radiotherapy with pharmacological inhibition of HSP90.

2016 POSTER DISCUSSION

Stereotactic body radiation therapy: a potential treatment option for colorectal liver metastases

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Background: Most of the patients with colorectal liver metastases are not eligible for surgery because of unfavourable tumor factors or due to patients' general condition. The introduction of stereotactic body radiation therapy (SBRT) has allowed physicians to add another local therapy to the treatment armamentarium of liver metastases. Local control, patient survival and toxicity were determined in our experience with stereotactic body radiation therapy for colorectal liver metastases.
Materials and Methods: SBRT was delivered with curative intent to 20 consecutive patients with colorectal hepatic metastases who were neither candidates for resection nor for radiofrequency ablation (RFA). Generally, the radiotherapeutic regimen consisted of 3 courses of 12.5 Gy with a prescription isodose of 65%. Median number of metastases was 1 (range, 1−3) and median size of metastases was 2.3 (0.7−6.2) cm. Toxicity was scored according to the Common Toxicity Criteria 3.0 (CTC). Local control rates were defined on tumor-based analysis.
Results: From December 2002 to July 2008, SBRT was given with curative intent to 20 patients with 31 colorectal liver metastases. In all patients the primary tumor was resected and liver metastases were irresectable and not amenable for radiofrequency ablation. Median follow-up was 26 months (range, 6−57 months). Local failure was observed in 9 out of 31 lesions after a median time interval of 22 months (range, 12−52 months). The actuarial two year local control and survival rate were 74% and 83%, respectively. Median overall survival was 34 months. Hepatic toxicity grade $\leqslant$2 (CTC) was reported in 18 patients. Two patients had an episode of hepatic toxicity grade 3 (CTC). No grade 4, 5 (death) or stomach, bowel, kidney or spinal cord toxicity was found.
Conclusions: SBRT has demonstrated to be a treatment option for patients with colorectal liver metastases, who were neither candidates for resection nor for RFA, with encouraging local control rates. The method seems to be safe concerning toxicity, if restrictions to normal tissue and patient selection are respected.

2017 POSTER DISCUSSION

Results from a phase I partial liver radiotherapy for patients with unresectable colorectal liver metastases

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Purpose: To report preliminary toxicity and response data from a phase I study of partial liver irradiation using highly conformal radiotherapy (CRT) for unresectable colorectal liver metastases (CRLM). Study has research and ethics committees approval REC: 06/Q0801/43.
Methods: Eligible patients have unresectable or medically inoperable CRLM and received all standard chemotherapy options, Childs score A and KPS >60 and signed informed consent. CRT is delivered hypofractionated in 10 fractions over 2 weeks. Planning target volume is patient specific according to tumour motion characterized on 4DCT and cine MRI. Dose is individualized according to volume of uninvolved liver treated in 3 dose bins: <30% = 40 Gy, 30−50% = 35 Gy, 50−70% = 30 Gy and to keep the estimated risk of liver toxicity <5%. Six patients to be entered in each dose bin. The endpoints are feasibility and toxicity using CTCv3 criteria. Radiation induced liver disease (RILD) grade 4 will stop recruitment. The trial sponsor is: Royal Marsden Hospital.
Results: From Nov 2006 to April 2009, 12 patients were recruited and all completed CRT. Mean age 67.9 years (range 44−85). All patients had chemotherapy median 2 cycles (range 1−4), 3 patients also had hepatic resection and 5 also had radiofrequency ablation. The tumor size ranged from 2.8cc to 395cc (mean 118cc). The CRT tumour dose ranged from 30 Gy to 40 Gy (average 34.6 Gy). Median follow-up was 8.4 months (range 1.5 to 28 months). No grade 3/4/5 related toxicity was observed at any time in follow up. No radiation-induced liver disease (RILD) was observed. Other toxicity within 3 months following CRT included grade 2: anaemia (1), pain (1), fatigue (2) and skin toxicity (1). In 11 evaluable patients, in-field response assessed using CT at 3 months was: partial response = 3, marginal response/stable disease = 6, progressive disease = 2.
Conclusion: In a heavily pretreated population this approach of individual dose CRT appears safe, and recruiting is continuing. Further dose escalation will be attempted. Longer follow up is required for assessment of late toxicity and efficacy.

2018 POSTER DISCUSSION

Benefit of radiotherapy dose escalation in localized prostate cancer with respect to expression of intrinsic markers of hypoxia

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Background: Dose escalation improves the efficacy of prostate cancer radiotherapy (RT) at the cost of increased toxicity. Tumor hypoxia causes radioresistance, so the benefit of RT dose escalation may be greater in more hypoxic cancers.
Methods: Cases had localized prostate cancer treated with neo-adjuvant androgen deprivation and radical RT at the Royal Marsden in two randomized trials of dose escalation (64 vs 74 Gy). Tumour expression of three markers (vascular endothelial growth factor (VEGF), hypoxia inducible factor-1Î± (HIF-1Î±), and osteopontin) was assessed immunohistochemically using a semi-quantitative scale by a uro-pathologist, and analyzed with respect to freedom from biochemical failure (FFBF) using the Phoenix definition. Expression of each marker was dichotomised about the median for analysis of the impact of dose-escalation on outcome.
Results: 201 cases with a median follow-up of 7 years were evaluable. Seven-year FFBF was 67% vs 40% (HR: 0.42, 95% CI 0.26−0.7, p = 0.001) for 74 Gy versus 64 Gy, respectively, among cases with high osteopontin expression, and 70% vs 82% (HR: 1.41, 95% CI 0.53−3.76, p = 0.49) for 74 Gy vs 64 Gy among cases with low osteopontin expression. The benefit of RT dose escalation was similar regardless of VEGF or HIF-1Î± expression.
Conclusion: These data generate the hypothesis that osteopontin expression could inform RT dose individualisation. If validated, patients