Materials and Methods: The present study investigates BIBW 2992 in models derived from HNSCC.
Results: In vitro, BIBW 2992 inhibited the proliferation of transfected Ba/F3 cells expressing the wild-type receptor with EC50 = 0.8 nM. Importantly, the compound showed similar potency on Ba/F3 cells expressing the EGFRvIII mutant receptor (EC50 = 0.5 nM). BIBW 2992 inhibited the proliferation of the HNSCC cell line FaDu with an EC50 of 7 nM. Cell cycle analysis by propidium iodide staining of treated cells showed a reduction of S-phase cells and a concomitant increase of G0/G1 cells at concentrations that match the EC50 values observed in the proliferation assays. In in vitro combination experiments BIBW 2992 shows at least additive activity when added to standard chemotherapeutics used in HNSCC patients (e.g. 5FU or taxanes). In vivo, potent, dose-dependent and long-lasting growth suppression and even tumor regressions were observed when mice carrying subcutaneous FaDu xenografts were treated daily p.o. with 20 mg/kg BIBW 2992. Short term treatment (3 days) of mice with BIBW 2992 before a single 20 Gy dose did not result in significant sensitization to radiotherapy. However, long term treatment with BIBW 2992 after a 20 Gy dose of radiation resulted in a tumor volume doubling time of 104 days thus slowing tumor growth by more than 3-fold. Combination of BIBW 2992 at suboptimal doses with the triple angiokinase inhibitor, BIBF 1120, resulted in improved efficacy in the FaDu model.
Conclusion: BIBW 2992 shows efficacy in human HNSCC models in vitro and in vivo. Clinical studies in this tumour type seem warranted.

5509 POSTER

Multicomponent coatings improve the biocompatibility of load-bearing implants

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Aim and Innovation: At this work was to estimate the influence of new multicomponent nanostructured coatings on the implant's osseointegration process. Titanium implants commonly used in orthopedics and dentistry integrate into host bone by a complex and coordinated process. The results of their application are completely satisfactory in many instances; however, are encountered the cases of the complications, which can be treated as the consequences of the insufficient biocompatibility of pure titanium. The signs of inflammation, thinning the skin, threat of the formation of sore and even fistulae can be seen. The danger of the similar complications development makes it necessary the search for titanium implants coatings, which would improve their biocompatibility and osseointegration. Osseointegration is a direct connection between living bone and the titanium implant at the level of the light microscope. Comparing with the previous studies new implants are studied in vivo under the conditions, when the replaced defect is located on the bone, which accomplishes motions with the large amplitude and with the large load.
Methods and Materials: of this investigation 48 rats femur model (250–300 g) were used. 3 types of implants were placed: one type had pure titanium core with TiC0.5 + 10%($Ca_{10}(PO4)_6(OH)_2$) composition coated on the surface. The average grain size is 10−40 nm. Another type had pure titanium core with TiC0.5 + CaO composition coated on the surface. The average grain size is 10−40 nm as well. The control was a pure titanium implant. An osteotomy was performed, and a 3 mm length of femur was removed. The implant was placed into the animal's tissue. Four screws fasten the implant to the femur's fragments fixing them. The animals were allowed full weight bearing without any mobility restrictions immediately postoperatively. Standard plain radiographs of the dissected bones were taken in lateral projections to ensure implant's stability. The rats were sacrificed and tissues investigated 5, 10, 15 and 30 days postoperatively.The degree of osseointegration correlates with the presence of osteocalcine, a differentiation marker of mature bone cells. The more rapidly increases osteocalcine concentration on the boundary between the bone and the implant, the more biocompatible implant appears.
Results: the effectiveness of implants considered in comparison with a control group of implants without nanostructured modification was proved by experimental models not only for stable, but also for moving with the large amplitude load-bearing implants.

5510 POSTER

Heparanase expression in the differentiation of follicular thyroid lesions: from laboratory to clinical practice

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The papillary, follicular, medullary and anaplastic variants of thyroid carcinoma can be promptly diagnosed by cytological criteria in material obtained by fine-needle aspiration (FNA) ultrasonography-guided. However, the distinction between follicular carcinoma and benign follicular adenoma needs histological demonstration of vascular or capsule invasion; therefore, they are cytologically grouped as undetermined tumors or suspect follicular neoplasm ("follicular pattern"). The aim of this study was to evaluate the immunohistochemical expression of heparanase, an endo-beta-glucoronidase, implicated in the process of tumor invasion in histological fields of thyroid follicular adenomas and carcinomas in an attempt to make a differential diagnosis of these neoplasms. Forty-nine thyroid follicular adenomas and 11 thyroid follicular carcinomas were evaluated, using the monoclonal antibody anti-heparanase by immunohistochemical reactions through the LSAB-peroxidase technique. The analysis was made by a quantitative digital computer-assisted method (Imagelab®). The immnunostaining analysis obtained showed a distinct pattern between follicular adenomas and carcinomas: while carcinomas showed positive immunostaining on neoplasic cells and negative immunostaining on coloid, adenomas showed an inverse pattern. This test presents sensibility of 91%, specificity of 86% and negative predict value of 98%. In conclusion, the association of positive heparanase on neoplasic cells and negative heparanase on coloid is a good immnuohistochemical test in the exclusion diagnosis of thyroid follicular carcinoma when compared to adenomas, with high sensibility, specificity and negative predict value.

5511 POSTER

The use of a radiophotoluminescent glass rod detector for the determination of cyberknife stereotactic radiosurgery system output factors

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Background: The Cyberknife (CK) radiosurery system can deliver single or several fractions of radiation doses to a well-defined small intracranial or extracranial target with a high precision. A radiophotoluminescent glass rod detector (GRD) system has recently become commercially available. The purpose of this study is to evaluate the possibility of the GRD as a new detector for dose measurement in small fields and high dose gradient regions. We introduce a novel method for measurement of 5 mm output factor for the CK using GRD. Although the concept of using GRD to determine output factors is not new, they have not gained measured output factor in water phantom The GRD holder is specially designed for this study to put into the water phantom for the irradiations.
Materials and Methods: In this study, the model GD-301 glass rod dosimeter (Asahi Techno Glass Corporation, Japan) and FGD-1000 automatic reader are used. The size of the model GD-301 is 1.5 mm in diameter and 8.5 mm in length. The relative output factor of CK collimators(5, 7.5, 10, 12.5, 15, 20, 25, 30, 35, 40, 50 and 60 mm) measurements with the GRD were compared with those with a PTW 60008 diode detector, PTW 31006 pinpoint type ionization chamber and a Gafchromic film (Type MD-55). The output measured with GRD, pinpoint chamber and diode was performed at a depth of 1.5 cm in water phantom. The GRD was irradiated in a water phantom using a holder stand, which was specially designed for this study. The holder is composed of the PMMA tube with a hole for GRD at 1.5 cm from its top. The water level was set precisely to the top of the holder and the axis of the beam aligned with holder axis in a way that the radiation beams pointed down vertically.
Results: The measured relative output factors with four dosimeters shown very similar results except for three smallest collimators (5, 7.5 and 10 mm). The mean value of the output factor for GRD in the 5 mm collimator is 0.705. Each dose point of GRD is presented by an average of 5GRD readings and their one standard deviation of each dose point is within ±1.0%.The pinpoint chamber output is approximately 11% lower than the corresponding GRD values at the 5 mm collimator. Because the pinpoint chamber had a larger effective volume, this most likely contributed to these differences. The GRD is 5.2% and 4.1% lower than diode in the 7.5 mm and 5 mm collimators, respectively. It is not obvious whether the difference

is due to the geometrical error in the diode positioning. The GRD results were in good agreement with those from the Gafchromic film for almost all the collimators.
Conclusions: For the GRD output factor measurements in water of CK system. It is found that GRD is a useful dosimeter for circular collimators smaller than 10 mm diameter, in good agreement with a Gafchromic film. Future study will be devoted to investigate for possibility of using GRD for quality assurance audit program of stereotactic radiosurgery units.

5512 POSTER

Expression of NHEJ genes in head and neck squamous cell carcinoma is associated with tumor response to 5-fluorouracil and cisplatin-based induction chemotherapy

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Expression of NHEJ genes in head and neck squamous cell carcinoma is associated with tumor response to 5-Fluorouracil and cisplatin-based induction chemotherapy.
Background: Concomitant chemoradiotherapy (CRT) or 5-Fluorouracil (5-FU) and cisplatin-based induction chemotherapy (IC), followed by CRT or radiotherapy (RT), are used to treat locally advanced head and neck squamous cell carcinoma (HNSCC). We studied the relationship between tumor expression of non-homologous end joining (NHEJ) repair genes (Ku80, Ku70 or DNA-PKcs) and their response to IC. The role of NHEJ in double-strand break (DSB) repair, genomic instability (HNSCC chromosomal rearrangements) and apoptosis suggests a possible role on tumor response to RT, 5-FU or cisplatin since all these agents induce DSBs.
Patients and Methods: In a Prospective Study, we evaluated the mRNA levels of Ku80, Ku70 and DNA-PKcs in 50 pre-treatment HNSCC biopsies by RT-PCR.
In a Retrospective Study, we evaluated Ku80 and Ku70 protein expression in pre-treatment HNSCC biopsies of an independent cohort of 52 patients by Immunohistochemistry (IHC) staining. Protein expression was assessed by morphometric image analysis, applying the HSI color model. This method makes it possible to measure the percentage of Ku80 and KU70 positive tumor cells present in a given tumor sample image.
To establish the relationship between Ku80, Ku70 and DNA-PKcs mRNA levels (or Ku70 and Ku80 protein expression) and response, we classified tumors in two groups according to response after IC. The responder group included patients with a reduction in tumor size higher than 50%, whereas the non-responder group included patients with an increase, stabilization or decrease in tumor size lower than 50%.
Results: Tumors included in the responder group had significantly higher mRNA levels for Ku80 ($p = 0.002$), Ku70 ($p = 0.005$) and DNA-PKcs ($p = 0.017$) than tumors in the non-responder group.
We also observed by IHC that the percentage of Ku80 and Ku70 positive tumor cells was significantly ($p = 0.021$, $p = 0.023$, respectively) higher in the responder group than in the non-responder group.
Conclusions: Ku80, Ku70 and DNA-PKcs expression in pre-treatment biopsies of patients with locally advanced head and neck squamous cell carcinoma is significantly associated with tumor response to 5-Fluorouracil (5-FU) and cisplatin-based induction chemotherapy.
In spite of these results additional independent studies will be necessary to validate the capacity of these genes to predict response to induction chemotherapy and to establish the best expression cut point.

5513 POSTER

Topical chemoprevention of skin cancer with dual inhibitors of 5-LOX and COX-2 via a microemulsion system

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Background: The cyclooxygenase (COX) and the 5-lipoxygenase (5-LOX) pathway have been suggested to play an important role in oral, colon, and other tissue carcinogenesis. However, it is unknown whether 5-LOX pathway contributes to skin carcinogenesis, and importantly whether combination of inhibitors of both pathways may have synergistic or additive effects of chemoprevention. In this study, we test topical combination application inhibitors of both pathways as a promising way for chemoprevention of skin cancer.
Material and Methods: Twenty four nude mice were intradermally inoculated with squamous cell carcinoma cells. Then these animals were divided into 3 groups (8 of each) to receive following treatments: (1) Celecoxib (a specific COX2 inhibitor); (2) combination of Zileuton (a specific 5-LOX inhibitor) and celecoxib; and (3) no treatment as a control. We investigated for the chemopreventive effects through topical application by a microemulsion system. Tumor growth continued to be measured for 15 days.
Results: The T50 (the time latency for the first 50% tumor to appear on all inoculated skin sites) were 3 days, 5days, and 6 days in control group, 6% celecoxib group, and 6% celecocib+6% zileuton group, respectively. Statistically, a significant difference of tumor growth was found between the control and two treatment groups. But the groups with the combined treatment had the best result, and showed an additive inhibitory effect on the incidence and growth of squamous cell carcinoma ($P < .001$).
Conclusions: The results clearly shows that both 5-LOX and COX2 play important roles in skin carcinogenesis, but a dual application of agents will significantly improve the results. We also found it would be a promising way to delivery celecoxib and zileuton through microemulsion system for topical inhibition of skin cancer. This is the first study for topical chemoprevention of skin cancer by combining inhibitors of 5-LOX and COX2.

5514 POSTER

Green tea extracts induce apopoptosis and inhibit in HGF-induced HNSCC progression in vitro

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Purpose: Activation of hepatocyte growth factor(HGF) and its receptor, c-Met, has been known to be involved in many human cancer development and progression. During the search for an effective molecule inhibitor of HGF/c-Met signaling, we have found that Epigallocatechin-3-gallate(EGCG), the major bioactive polyphenol present in green tea, might inhibit HGF/c-Met signaling. Studies were performed to address whether EGCG inhibit HGF-dependent tumor proliferation and invasion in HNSCC.
Method: We performed RT-PCR and Western blot of HNSCC cell line. Proliferation assay, dispersion assay, wound healing assay, and invasion assay were performed in HGF 0, 10, 30 ng/mL HGF10+EGCG 1 μM, HGF10+EGCG10 μM, HGF30+EGCG1 μM, HGF30+EGCG10 μM. RT-PCR and zymography were performed to examine the roles of MMP-2 and MMP-9, as well as the relationship between HGF and MMPs in FaDu invasiveness. In addition, we confirmed HGF-mediated plasmin activation. We performed Tunnel assay, DNA fragmentation analysis, Annexin V staining, and FACS analysis for apoptotic effect of EGCG in HNSCC.
Results: Exogenous HGF significantly enhanced the growth of HNSCC cell and this phenomenon was inhibited by EGCG in dose-dependant manner. ($p < 0.05$) EGCG inhibited HGF-induced scattering of HNSCC cell. EGCG inhibited HGF-mediated migration and invasion of HNSCC cell in dose-dependant.($p < 0.05$). EGCG inhibits the HGF-Met-uPA-Plasmin network and MMP2, 9. We confirmed EGCG induced apoptotic phenomenon in Tunnel assay, Annexin V staining, DNA fragmentation analysis and FACS.
Conclusions: Inhibition of HGF/Met signaling by EGCG leads to decrease of proliferation and invasion in vitro, suggesting the possible use of EGCG in HNSCC associated with downregulation of HGF/Met signaling and the HGF-Met-uPA-Plasmin network and MMP2, 9.

5515 POSTER

Comparison of the efficacy and safety of miconazole 50 mg mucoadhesive buccal tablets to those of miconazole 500 mg gel in the treatment of oropharyngeal candidiasis: a prospective, randomised, single blind, multicenter, comparative, phase III trial in patients treated with radiotherapy for head and neck cancer

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Background: Topical antifungal treatments are recommended as first line therapy for oropharyngeal candidiasis (OPC) in cancer patients. However, they are not used because of multiple daily dosing, bad taste and poor acceptance by patients. Miconazole 50 mg mucoadhesive buccal tablet (MBT) is a new delivery system that was reported to produce rapid and prolonged effective concentrations of miconazole in the mouth. Its pharmacokinetic profile is well suited to the treatment of OPC.
Patients and Methods: This prospective, single blind, randomised, comparative, multicenter trial was aimed at comparing the efficacy and safety of a 14-day treatment with MBT once daily to those of miconazole 500 mg oral gel (MOG) administered in 4 divided doses in head and neck cancer patients having undergone radiation therapy. Primary end point was clinical success at day 14. Secondary endpoints included clinical success at day 7, clinical cure, improvement in clinical symptoms, mycological cure, relapse rate and safety.
Results: A total of 282 were enrolled. Patients from both groups were not different at baseline, except for the extent of lesions and severely impaired