tyrosine kinase, has been demonstrated in non-small cell lung carcinoma patients with EGF receptor mutations, and so these mutations are a useful marker(s) to find responders to this drug. However recent studies showed that the EGF receptor gene mutation is rare in squamous cell carcinomas of the esophagus and head and neck regions. In the present study we investigated the relationship between BRAK expression and gefitinib efficacy for tumor suppression.
Material and Methods: HNSCC cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM) containing 10% fetal bovine serum. Nearly confluent cells were cultured overnight in serum-free DMEM. After starvation, they were incubated with or without EGF (10 ng/ml) and/or gefitinib (1 μM). HSC-3 cells were subcutaneously injected into athymic nude mice. Tumor cell-xenografted mice were daily administered gefitinib (50 mg/kg) orally. In some experiments, tumor cells were introduced BRAK ShRNA expressing vector to knockdown BRAK mRNA expression and established stable transformants.
Results: Gefitinib attenuated the effect of EGF, or even stimulated BRAK mRNA expression of HNSCC cells *in vitro*. Oral administration of gefitinib significantly ($P < 0.001$) reduced tumor growth of xenografts in female athymic nude mice accompanied by increased in BRAK expression specifically in tumor tissue. Introduction of BRAK ShRNA vector reduced both the expression of BRAK in the cells and the antitumor efficacy of gefitinib *in vivo*.
Conclusions: Our results indicate that oral administration of gefitinib reduced tumor size, at least in part, through elevation of BRAK expression. Thus, the use of gefitinib for treatment of patients with HNSCC in whom there is an inducing effect of the drug on the BRAK expression in cancer cells in culture may be advantageous. Furthermore, BRAK may be a promising molecule for gene therapy of HNSCC.
This work was performed in collaboration with Drs. Takahide Taguchi, Yukari Imagawa-Ishiguro and Mamoru Tsukuda, Department of Biology and Function in the Head and Neck, Yokohama City University Graduate School of Medicine.

8525 POSTER

Prediction of pathological response of preorerative 5-fluorouracil-based chemotherapy for oral cancer

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Background: The response of chemotherapy is individually different in patients with oral squamous cell carcinoma (OSCC). Prediction of chemotherapy response is very important to select adequate therapy for every patient. We retrospectively investigated the relationship between chemotherapy response and expression of biomarkers in OSCC patients who received 5-fluorouracil (5-FU) based chemotherapy and following radical surgery. The aim of this study is to make the formula which predicts chemotherapy sensitivity using some biomarkers.
Material and Methods: Retrospective analysis of biomarker expressions in biopsy specimen was performed immunohistochemically in 95 OSCC patients. These received 5-FU based chemotherapy such as TS-1®+cisplatin, UFT®+cisplatin, etc. We use 17 biomarkers including dihydropyrimidinedehydrogenase (DPD), thymidylate synthase, EGFR, cyclinD1, Ki-67, c-Met, MMP-1, MMP-2, MMP-9, TIMP-1, TIMP-2, Bax, Bcl-2, CD25, Foxp-3, Caveolin-1. The expression of these biomarkers were evaluated by staining intensity or percentage of positive cells. Pathological effects were evaluated in surgical specimens. We compared these 2 factors and selected significant biomarkers which had association with chemotherapy response. Statistical analysis was performed using Spearmans' correlation coefficient test and logistic regression model.
Results: There was a statistically significant relation between the expression of five biomarkers (DPD, VEGF, MMP-2, Ki-67 and Bcl-2) and the pathological response for 5-FU based chemotherapy. The formula which predicts chemotherapy sensitivity was made by logistic regression model consisted of above five markers. We applied this formula to another 14 OSCC patients for verifying its accuracy. In consequence, the accuracy rate was 85.7%.
Conclusions: The expression of DPD, VEGF, MMP-2, Ki-67 and Bcl-2 were independent predictor for sensitivity of 5-FU based chemotherapy. The combination of these biomarkers was useful for predicting chemotherapy response. The formula was applicable for OSCC patients before chemotherapy and realized high accuracy to predict chemotherapy response.

8526 POSTER

The tumour volume for F-18 fluorodeoxyglucose predicts for response to treatment and progression free survival biomarker in head and neck cancer

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Purpose: To evaluate the prognostic value of metabolic tumor volume measured on 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging and other clinical factors in patients treated for locally advanced head-and-neck cancer (HNC) at a single institution.
Materials and Methods: Between June 2005 and August 2008, fifty nine patients with HNC who underwent pretreatment FDG-PET studies received neoadjuvant chemotherapy and radiation therapy. Metabolically active tumor regions were delineated on pretreatment PET scans by a fixed SUV of 2.5. We evaluated the relationship of 18F-fluorodeoxyglucose-PET maximum standardized uptake value (SUV) and metabolic tumor volume (MTV) with response to treatment, progression-free survival (PFS) and overall survival (OS).
Results: The average SUVmax was 8.9 (range, 1.4−78.0) and the mean MTV was 23.5 cm3 (range, 1.2−170.8) for all patients. Higher MTV was associated with an increased risk of lymph node metastasis at diagnosis ($p = 0.028$) and response to treatment ($p = 0.026$). A Cox proportional-hazards model for progression free survival from head and neck cancer was used to evaluate sex, age, organ, stage, T-stage, lymph node metastasis, MTV, and SUVmax and neoadjuvant chemotherapy type. The results indicated that MTV was the only significant independent factor ($p = 0.021$). A higher MTV of 9.3 cm^3 (median MTV) was significantly associated with an increased hazard of recurrence (2.19-fold, $p = 0.007$). We did not find a significant relationship of maximum SUV, stage, or other clinical factors with response to treatment or PFS or OS.
Conclusions: Metabolic tumor volume is an adverse predictive factor for treatment response and disease progression in HNC. MTV is a direct measure of tumor burden and is a potentially valuable tool for risk stratification and guiding treatment in future studies.

8527 POSTER

A phase II trial of erlotinib after gemcitabine plus platinum-based chemotherapy in patients (pts) with recurrent and/or metastatic nasopharyngeal carcinoma (NPC)

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Background: Although chemotherapy with a platinum compound and gemcitabine (G) is effective in recurrent and/or metastatic NPC, the outcome remains poor with time-to-progression (TTP) <1 year. The epidermal growth factor receptor (EGFR), expressed in 85% NPC, is associated with poor prognosis. We conducted a phase II study to determine the efficacy of the EGFR tyrosine kinase inhibitor erlotinib, given as maintenance therapy, following cisplatin (C) or carboplatin (Ca) + G in pts with recurrent and/or metastatic NPC.
Methods: Pts were treated with up to 6 cycles of chemotherapy (G 1000 mg/m^2 day 1 and 8, C 70 mg/m^2 day 1 or Ca AUC = 5 day 1 if contraindication to C) every 3 week. Pts were switched to erlotinib 150 mg PO daily Q4W after 6 chemotherapy cycles, or before if they progressed on chemotherapy. Primary endpoint was TTP in non progressive disease (PD) pts after 6 chemotherapy cycles and treated with maintenance erlotinib. EBV DNA plasma levels were measured using qRT-PCR.
Results: Of 20 pts, 1 pt never started chemotherapy. Median follow-up was 5.8 months. Pts characteristics were: M:F = 13:7, asian:non-asian = 14:6, median age 56 [range 32−72], PS 0:1 = 10:10, locoregional recurrent:metastasic = 6:14. With G, 8/20 pts (40%) and 12/20 (60%) were treated with C and Ca, respectively. After 96 chemotherapy cycles, the most frequent grade 3/4 adverse events (AE) were neutropenia (63%), thrombocytopenia (47%) and anemia (21%). Of the 19 pts evaluable for response to chemotherapy, 7 pts had a PR (35%), 11 SD (58%) and 1 PD (6%). Of them, 15 pts received 36 cycles of erlotinib (median = 2, range = 0−6). The most frequent grade 3 AE related to erlotinib were lymphopenia (26%), acneiform rash (20%), hand-foot syndrome (13%), neutropenia (13%) and fatigue (7%). No grade 4 toxicity was observed. Of 11 pts evaluable for response to erlotinib, all progressed except 3 pts (27%) with stable disease for 3, 4 and 7 months. Median TTP was 6.3 months for all 17 evaluable pts, and 6.9 months for 13 pts with no PD after 6 chemotherapy cycles. One-year overall survival was 80% for all pts. No correlation between EBV DNA plasma levels or kinetics and clinical outcome was detected.
Conclusions: Maintenance or 2nd line therapy with erlotinib post-chemotherapy is not effective in recurrent and/or metastatic NPC. Historical