1105 POSTER

Association of ABCC2 Genotype With Response and Progression-free Survival of First-line FOLFIRI in Japanese Patients With Advanced Colorectal Cancer

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Background: This hypothesis-generating retrospective study examined the effects of genetic polymorphisms in genes related to both irinotecan pharmacokinetics and pharmacodynamics on efficacy of combined therapy consisting of irinotecan, 5-fluorouracil, and leucovorin (FOLFIRI).
Material and Methods: Japanese patients with advanced colorectal cancer who received first-line FOLFIRI were studied, since this regimen is frequently used because of its high effectiveness for the treatment of such patients. All patients harbored *UGT1A1*1/*1*, **1/*6*, or **1/*28* genotypes that were proven to show similar irinotecan pharmacokinetics and efficacy of FOLFIRI, ensuring the subjects having similar genetic backgrounds of *UGT1A1*. Direct sequencing was conducted to analyze genetic polymorphisms in genes related to irinotecan pharmacokinetics including ATP-binding cassette, sub- family C, member 2 (*ABCC2*), and irinotecan pharmacodynamics such as topoisomerase 1 (*TOP1*).
Results: A total of 61 patients with advanced colorectal cancer received first-line FOLFIRI from June 2003 through April 2008. The overall response rate and median progression-free survival in FOLFIRI were 43% and 7.5 months, respectively. Overall response rate was higher in patients with CC genotype at −24 in A*BCC2* than others (P = 0.0313). Median progression-free survival was the longest in patients with CC at −24 in *ABCC2*, followed by those with CT and TT (P = 0.0091). Clear gene-dose effects were observed between −24C>T and median progression-free survival. Other polymorphisms in all genes tested were not correlated with the efficacy of FOLFIRI.
Conclusions: We thus found the association between −24C>T in *ABCC2* and efficacy of FOLFIRI. Our findings suggest that pharmacogenetics of *ABCC2* can be used to predict the irinotecan efficacy.

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Cysteine Rich 61 (CCN1) Protein Expression as a Predictive Marker in Endometrial Cancer

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Background: Cysteine rich 61 (Cyr61/CCN1) is an important player in tumorigenesis due to its pro-angiogenetic activities. Cyr61 undergoes alternative splicing resulting in two different mRNAs. Hypoxia triggers the predominant expression of the solely protein-generating mRNA. Cyr61 expression studies in EC found both, a downregulation as well as an overexpression of the protein. We studied the expression of Cyr61 and its splicing isoforms in EC.
Methods: Cyr61 protein expression in 138 tissue samples originating from EC patients was evaluated by immunhistochemistry (IHC) and correlated to clinicopathologic factors separating histological types I and II. Survival of tumour patients was calculated by using Kaplan–Meier curves and Log-rank-test. Expression of both Cyr61 mRNAs was investigated by real-time PCR. Immunhistochemical results were correlated to expression levels of Cyr61 mRNAs.
Results: Cyr61 overexpression was detected in 15% of endometrial cancer samples. Multivariant-analyses confirmed correlation of high protein expression levels (IHC) with lymph node metastasis, lymphangioinvasion and tumour-grading. Patients with an overexpression of Cyr61 showed lower overall-survival and shorter relapse-free-survival compared to patients exhibiting low or moderate Cyr61 expression. We could not find any significant correlation between immunhistochemistry and expression of the protein-generating mRNA.
Conclusion: Overexpression of Cyr61 in EC correlates well with poor survival, lymph node metastasis, lymphangioinvasion and tumour-grading. Therefore, it could represent a new molecular marker in predicting survival of patients with estrogen-dependent EC. Posttranslational modifications may account for the discrepancy of Cyr61 protein expression examined by IHC and no significant correlation with expression levels of the protein-generating Cyr61 mRNA obtained by real-time PCR.

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Phase I Study of Multiple Peptides Vaccination in Patients With Advanced Bile Duct Cancer

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Background: The prognosis of patients with advanced bile duct cancer is extremely poor and there is only few standard treatment. Recently, the safety and the clinical efficacy of vaccination with cancer-testis antigen derived peptides has been reported in some clinical trials. In ths study, we investigated the safery, immunological responses and anti-tumour effect of vaccination with four cancer-testis antigen derived peptides which we previously identified for patients with advanced bile duct cancer.
Material and Methods: Patients with advanced bile duct cancer who had unresectable tumours to be refractory to chemotherapy were vaccinated once a week for four weeks of a treatment cycle and continued vaccinations until their diseases were progressed. On each vaccination day, the HLA-A*2402 restricted epitope peptides, which were derived from four cancer-testis antigens, DEP domain containing 1 (DEPDC1), lymphocyte antigen 6 complex locus K (LY6K), insulin-like growth factor (IGF)-II mRNA binding protein 3 (IMP-3) and TTK protein kinase (TTK) mixed with Montanide ISA-51, SEPPIC were administered by subcutaneous injection. The adverse events were assessed by Common Terminology Criteria for Adverse Events (CTCAE) version 3 and the immunological responses were monitored by an enzyme-linked immunospot (ELISPOT) assay or a flow cytometry. The clinical effects were observed by CT scan, progression-free survival (PFS) and overall survival (OS).
Results: Nine patients (4 males, 5 females, median age 70 years, range 59−78) were enrolled and treated at doses of 0.5 mg each of four peptides (n = 3), 1 mg each (n = 3) and 2 mg each (n = 3). Eight of 9 patients developed grade 1 or 2 local skin reactions in the injection sites. No grade 3 or 4 adverse events were observed. Peptides-specific T cell immune responses were observed in seven of 9 patients and clinical responses (stable disease or objective response) were observed in six of 9 patients. The median PFS after the first vaccination was 156 days and the median OS was 380 days. The patients who developed grade 2 local skin reaction showed the longer survival time (p = 0.0027).
Conclusions: The cancer vaccine therapy using these four peptides was well tolerated and appeared to provide some clinical benefit. This result warrants further Phase II clinical study.

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DEAD/H (Asp-Glu-Ala-Asp/His) Box Polypeptide 3, X-linked is a CD133+ Tumour-specific Protein and Induces Antitumour Immunity

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Background: Cancer cells that exclusively maintain the ability of self-renewal and differentiation are termed cancer stem cells (CSC). It is still controversial if the classical CSC hierarchy exists in all of solid tumours, however, accumulating evidence suggests that heterogeneity within cancer cells exists and that cancer survives as the cells with CSC features during potentially lethal stresses, including chemotherapy, radiation treatment, and molecular targeting therapy. Although it is necessary to eradicate CSC to obtain cure of cancer, effective treatment has not been elucidated. It has been demonstrated that most of immunogenic tumour-associated antigens belong to cancer/testis (CT) antigens. One of the reasons why CT antigens are immunogenic is that they are unlikely to maintain peripheral tolerance, owing to restricted expression in the testis and in immortal malignant cells. It was reported that CT antigens are mainly expressed in CSCs. Since CSC are highly immortal, it is possible that they possess immunogenic antigens that are not expressed in differentiated cancer cells or normal epithelial cells, and that these antigens may be ideal therapeutic targets for cancer treatment.
Materials and Methods: Tumour cells: B16F10 is a melanoma of B6 mice origin and was maintained *in vitro*. $CD133^+$ tumour cells were isolated with PE-conjugated anti-CD133 mAb and anti-PE microbeads™ and autoMACS™. All of the human cancer cell lines, including HCT116, 87.5, S2, A549, MCF-7, and WM115 were obtained from ATCC.
Proteome analysis: Proteome analyses of $CD133^+$ and $CD133^-$ tumour cells were carried out by two-dimensional protein gel electrophoresis. Expression of DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 3, X-linked (DDX3X) was analyzed with immunoblotting assay.