caspase inhibitor of all known IAP (inhibitor of apoptosis) family members. This study was designed to assess the pattern of expression and the prognostic value of XIAP in radically resected non-small cell lung carcinoma (NSCLC) patients.
Method: The expression of XIAP and its relationship with clinicopathologic parameters (patient age, TNM stage, TNM-pT, TNM-pN, histologic type, VEGF expression, microvessel density, PCNA index) and overall survival were analysed with formalin-fixed, paraffin-embedded blocks from eighty cases of NSCLC. In addition, the apoptotic index (AI) was also assessed.
Results: In a regard to histologic type, squamous cell carcinoma (SCC) showed XIAP expression in 91.3% (42/46) and adenocarcinoma (AC) in 61.8% (21/34). The difference was significant ($p = 0.001$). There was no correlation between XIAP expression and other parameters. In the group of AC, XIAP expression showed the signifcant correlation with older age group $\geqslant$58 years and VEGF expression ($p = 0.028$, $p = 0.014$, respectively). The AI in the group with or without XIAP expression were $2.5 \pm 4.9\%$ and $18.5 \pm 28.9\%$, respectively ($p = 0.001$). Both groups just aforementioned showed no significant difference in median survival time (42.5 months, 29.8 months, respectively).
Conclusion: This study suggests that the XIAP expression in NSCLCs could have relation to inhibition of apoptosis, and show differential expression according to histologic type. However, its prognostic role during the progression of NSCLC needs to be further defined.

1186 PUBLICATION

Expression of MAGE-D4 is correlated with tumor-cell proliferation of non-small cell lung cancer

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Purpose: MAGE-D4, originally named as MAGE-E1, is a novel MAGE family gene that was highly expressed in malignant tumors, but less expressed in normal tissues. in the present study, we examined expression and intracellular localization of MAGE-D4 protein in NSCLC, and revealed the following findings: 1) expression of MAGE-D4 mRNA was up-regulated in tumor tissues compared with the normal lung, 2) intracellular distribution and morphological changes according to cell-cycle of MAGE-D4 was similar to those of the tubulin, 3) enhanced MAGE-D4 expression was correlated with higher proliferative activity.
Experimental Design: Expression of MAGE-D4 protein was estimated by immunohistochemistry. MAGE-D4 mRNA expression was also studied by quantitative reverse transcription–PCR (RT-PCR).
Results: We assessed MAGE-D4 expression in NSCLC tissues. MAGE-D4 expression was up-regulated in tumor tissues compared with normal lung tissues (mean MAGE-D4/GAPDH values, 0.035 for tumor tissues and 0.009 for normal lung tissues; $P = 0.002$), but no significant difference in MAGE-D4 expression according to the pathologic stage. Proliferative activity of tumor cells was significantly higher in high MAGE-D4 tumor (mean proliferative indices, 58.3 for high MAGE-D4 tumor and 34.0 for low MAGE-D4 tumor; $P < 0.001$). In addition, high MAGE-D4 expression was more frequently seen in squamous cell carcinoma than in adenocarcinoma ($P = 0.008$), and less frequently in well-differentiated tumors than in moderately to poorly differentiated tumors ($P = 0.036$). There was no difference in the postoperative survival between low and high MAGE-D4 patients (5-year survival rates, 65% and 69%, respectively; $P = 0.742$).
Conclusion: MAGD-D4 co-localized with beta-tubulin in a cell cycle specific manner and may play some roles in cell division. MAGE-D4 was correlated with tumor cell proliferation whereas MAGE-D4 status failed to have a prognostic value, suggesting that MAGE-D4 could be a molecular target for prevention and therapy of NSCLC.

1187 PUBLICATION

Combined therapy with radiation and S-1, an oral new 5-FU prodrug, is markedly effective against non-small cell lung cancer xenografts in mice

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Background: Radiochemotherapy is usually used to treat advanced (Stage III to IV) non-small cell lung cancer (NSCLC). Cisplatin (CDDP)-based regimens are often used for chemotherapy. S-1 is a novel oral 5-fluorouracil (5-FU) derivative that combines tegafur with Gimeracil, which inhibits the degradation of 5-FU in the liver and tumors, and oteracil, which reduces 5-FU-induced gastrointestinal toxicity. S-1 has been demonstrated to be active against advanced NSCLC. We investigated whether a combination of oral S-1 and tumor irradiation potentiated antitumor activity against human NSCLC xenografts in vivo.
Methods: Human lung cancer xenografts, designated LC-11 and Lu-99, were used. Tumor fragments were implanted *s.c.* into the right leg of nude mice. Two weeks later, the mice were treated with oral S-1 (8.3 mg/kg) once daily for 14 days or local tumor irradiation (2 Gy and 5 Gy) on day 1 and 8, or both. As reference regimens, CDDP (5 mg/kg, day 1) or UFT (tegafur plus uracil, 17.5 mg/kg for 14 days) was administered according to similar schedules in the same model. The effects of the treatment were evaluated on the basis of the delay in tumor growth.
Results: Combined treatment with S-1 plus 2 Gy tumor irradiation was significantly more effective against both lung tumors than S-1 alone and 2 Gy irradiation alone, and the effect of this combination was nearly equivalent to that of 5 Gy irradiation alone. A combination of S-1 plus 2-Gy irradiation was also more effective than the same dose of irradiation plus CDDP or UFT against LC-11 tumors. Gimeracil was found to potentiate sensitivity to lower-dose irradiation, whereas gimeracil alone had neither antitumor nor toxic activity, suggesting that this component of S-1 was involved in enhancing the response to irradiation.
Conclusion: Our preclinical results strongly suggest that radiochemotherapy with the new oral 5-FU derivative S-1 plus low-dose tumor irradiation would contribute to the improved treatment of patients with advanced NSCLC.

Melanoma and Sarcoma

Oral presentations (Mon, 31 Oct, 9.15–11.15)
Melanoma and sarcoma

1188 ORAL

Final data of the EORTC phase 1 study determining safety of Caelyx in combination with Ifosfamide in previously untreated adult patients with advanced or metastatic soft tissues sarcomas

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Background: Caelyx seems to have the same efficacy in adult soft tissue sarcomas as Doxorubicin with an improved toxicity profile. It could thus be an alternative to Doxorubicin and may well be easier to combine with agents such as Ifosfamide. The present phase 1 study evaluated the toxicity of combining Caelyx with Ifosfamide as 1st line treatment for patients (pts) with advanced and/or metastatic soft tissue sarcomas.
Material and methods: Eligibility included soft tissue sarcomas progressing within 6 weeks, no previous chemotherapy for advanced disease, WHO PFS <2, age 19–69 years and adequate cardiac, liver, renal and haematological function. Five dose levels were studied: Caelyx 30 mg/m^2 (level 1–4) or 40 mg/m^2(level 5) 1-h infusion d 1 q 3 w + Ifosfamide (with Mesna) at Xg/m^2/4-h d 1–3 q 3 w at 5 doses: Level 1: X = 1.7 g; level 2: X = 2 g; level 3: X = 2.5 g; level 4 and 5: X = 3 g. Cohorts of 3 pts were entered at each dose level unless a DLT occurred, defined as ANC $<0.5 \times 10^9$ lasting for 7 days or for 3 days + fever ($\geqslant$38.5 °C), grade 4 thrombocytopenia, any grade 3–4 toxicity except nausea, vomiting and alopecia, and any toxicity requiring a 2 w delay. In case of DLT in 1/3 pts a new cohort was added. Toxicity was evaluated by CTC. Non-evaluable pts were replaced.
Results: 28 pts have been included. Median age was 60 years (29–69). Four pts were included at dose level 1, 8 pts at level 2, 3 pts at level 3, 6 pts at level 4, and 7 pts at level 5. No DLT was observed at level 1–4. Four pts with DLT were observed at dose level 5: Febrile neutropenia, renal insufficiency, dyspnoea, confusion and allergy. Otherwise toxicity was generally acceptable and primarily granulocytopenia and leucopenia. Non-haematological toxicities >grade 2 were few. PPE >grade 1 was not seen. At present response is evaluable in 19 pts of which 2 obtained PR and 13 SD.
Conclusions: Combined Caelyx and Ifosfamide seems to be feasible in pts with advanced soft tissue sarcomas allowing administration of Ifosfamide at a dosage similar to that used when Ifosfamide is given alone. The recommended dose is Caelyx 30 mg/m^2/1-h d 1 + Ifosfamide (with mesna) at 3 g/m^2/4-h d 1–3 q 3 w.