increased number of recurrences within 36 months in the group with persisting levels of M30 (4/7 versus 2/24, p = 0.032). Tumor surgery led to decreased M65 serum measurements postoperatively in a subgroup of patients (19/31), in contrast to 12 patients who revealed higher M65 levels postoperatively. MRD was proven in 10% (2/19) of the first group and 50% (6/12) of the second group (p = 0.028).
Conclusions: Tumor surgery clearly has an effect on postoperative serum concentrations of the M65 antigen indicating that perioperative determination of serum concentrations of this antigen seem to constitute a marker of postoperative systemic residual tumor load in colorectal cancer patients. The difference in early and advanced tumor stages as well as in preoperative and postoperative serum concentrations of the M30 antigen seems to represent an interesting marker of residual tumor load and early tumor recurrence.

6124 POSTER

Cetuximab specific IgE antibodies can predict cetuximab-induced anaphylaxis

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Background: Cetuximab is a chimeric mouse-human IgG1 monoclonal antibody against the epidermal growth factor receptor. This drug is used for the treatment of colorectal cancer and squamous-cell carcinoma of the head and neck. Severe hypersensitivity reactions to cetuximab have been described with prevalences varying from 1.2% to 22% depending on the area of the world. An American study has shown that IgE specific for galactose-α-1,3-galactose are present in serum before therapy of most subjects who had a hypersensitivity reaction to cetuximab.
The main goal of our work was to confirm that IgE specific antibodies against cetuximab were involved in the clinical reaction observed in our hospital (prevalence of severe reaction estimated at 7%). The predictive value of cetuximab specific IgE was evaluated.
Material and Methods: IgE anti-cetuximab were measured using home made enzyme-linked immunosorbent assay (ELISA). A technical cut-off value of 10 arbitrary units IgE (AUE) was calculated from healthy blood donors. We analyzed retrospectively serum samples from 60 patients treated with cetuximab in Francois Baclesse Anticancer center.
Results: Among the 60 cetuximab-treated subjects, 14 had a hypersensitivity reaction (grade 2, 3 or 4) to the drug. IgE antibodies against cetuximab were found in 13/14 pretreatment samples. 12 out of 46 subjects without hypersensitivity reaction had IgE antibodies. Sensitivity and specificity of this test were 92.9 and 73.9% respectively. The positive predictive value was 52% and more interestingly, the negative predictive value was 97.1%.
Conclusions: Cetuximab IgE specific antibody detection could represent a valuable test and help the prescriptor to select an alternative treatment for patients with high risk of hypersensitivity reaction when available.

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6125 POSTER

Topoisomerase-1 (Topo1) as a predictive and prognostic factor in colorectal cancer chemotherapy

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Background: In the FOCUS-1 trial, analysis of primary tumour Topo1 immunohistochemistry (IHC) in 1313 patients with metastatic colorectal cancer (MCRC) receiving 5-fluouracil (FU), oxaliplatin (Ox) and irinotecan (Ir) showed higher Topo1 expression to be associated with worse outcomes with FU alone but increased benefit from Ir/Ox (Braun et al, JCO 26:2690−8, 2008). In FOCUS-2, 459 elderly/frail patients with MCRC were randomised to first-line FU, OxFU, Capecitabine (Cap) or OxCap. Topo1 expression in FOCUS2 patients was assessed to see whether the results of the FOCUS-1 study were confirmed, and whether any predictive association with Ox is affected by the fluoropyrimidine (FP) platform.
Methods: Tumour blocks were retrieved. 5 μm slices of tissue microarrays or whole sections were stained for Topo1 (Novocastra antibody) and scored as low (<10% nuclei staining) or mod/high (>10% nuclei). The Mantel-Haenszel log-rank test was used to calculate hazard ratios (HR) and 95% confidence intervals (CIs) to assess the effect on progression free survival (PFS) and overall survival (OS) when Ox is added to FU or Cap. Interactions between treatment effects and Topo1 were tested using the likelihood ratio and the magnitude of interactions was assessed using the ratio of HRs.
Results: Topo1 results were obtained for 361 (79%) patients. Overall, adding Ox to either FP improved the PFS (HR 0.78, 95%CI [0.62−0.96], p = 0.02), with a non-significant impact on OS (HR 0.88 [0.70−1.24], p = 0.27). In prognostic analysis, mod/high Topo1 was associated with worse PFS in FP-alone treated patients (HR 1.20 [0.87−1.65]), but better PFS in OxFP-treated patients (HR 0.79 [0.55−1.13]). In predictive analysis, mod/high Topo1 was associated with a benefit for adding Ox (PFS: HR 0.71 [0.55−0.91]; OS: HR 0.84 [0.65−1.10]), whilst patients with low Topo1 gained no benefit (PFS: HR 0.97 [0.65−1.46]; OS: HR 1.03 [0.66−1.60]). These results, although not independently significant, are fully consistent with the results of FOCUS-1. The interaction was more pronounced with OxFU/FU (ratios of HRs: PFS = 1.63 [0.83−3.18]; OS = 1.42 [0.69−2.94]) than with OxCap/Cap (ratios of HRs: PFS = 1.20 [0.60−2.4]; OS = 0.98 [0.47−2.06]). For comparison, the ratios of HRs for OxFU/FU in FOCUS-1 were PFS = 1.35 [0.99−1.83], OS = 1.35 [1.05−1.74].
Conclusion: FOCUS-2 is consistent with FOCUS-1, with similar magnitude of prognostic and predictive effects for Topo1 IHC in relation to FU and Ox. Less pronounced effects are seen when Cap is used as the FP platform.

6126 POSTER

Presence of K-RAS and BRAF oncogenic mutations sensitise colorectal tumours to TRAIL induced apoptosis: evidence from cell and animal models translated to the clinic

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Background: Most data on the therapeutic potential and expression of TRAIL in colorectal cancer has come from *in vitro* studies using tumour cell lines. To gain a clearer understanding about the susceptibility of patient tumours to TRAIL, we derived primary human cancer epithelial cells [1]. Increased apoptosis was observed in both primary PAP60 and MIH55 after treatment with SuperKiller TRAIL. Treating patient tumour xenograft/SCID mouse models with Killer TRAIL *in vivo* for 5 consecutive days suppressed tumour growth, although less efficiently compared to *in vitro* experiments. Sensitization to TRAIL induced apoptosis by RAS has been previously shown by our lab [2] and by others. We have presented evidence that this effect is usually mediated by TRAIL receptor DR4 and DR5 overexpression and/or redistribution in cell models [3].
Materials and Methods: Primary colorectal tumour cells, colorectal cell lines, mouse xenographs and colorectal clinical samples were either treated with recombinant TRAIL and/or analysed for the presence of oncogenic mutations and DR4, DR5 expression.
Results: We present evidence that DR5 as the most frequently upregulated DR in clinical samples of colon cancer. Furthermore, the presence of K-RAS and BRAF mutations in the tumour may directly or indirectly enhance DR expression, potentially sensitising these otherwise resistant tumours to TRAIL-based therapies [4].
Discussion: Mutations on K-RAS and BRAF oncogenes have been shown in many studies to be associated with resistance to several targeted therapeutics and combinations. TRAIL-based therapeutics, other as mono- or combination therapy could provide a promising alternative for K-RAS/BRAF bearing colorectal tumours.

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