Results: 86 patients were included. M/F = 44/42, median age = 67 (41−78), median number of previous lines of chemotherapy = 2 (1−5). In the subgroup of 52 (60%) *KRAS* wt patients, *BRAF* mutation was associated with a trend toward lower response rate (RR 1/10, 10% vs 12/42, 29%; OR: 3.86 [95%CI: 0.44−33.88], p = 0.224) and with significantly shorter PFS (HR: 2.33 [95%CI: 1.12−4.84], p = 0.023) and OS (HR: 3.51 [95%CI:1.55−7.98], p = 0.003). *KRAS* wt patients with higher AR expression showed a trend toward better RR (OR: 0.94 [95%CI: 0.88−1.02], p = 0.119) and PFS (HR: 0.971 [95%CI:0.938−1.005], p = 0.095) that translated into significantly longer OS (HR: 0.950 [95%CI: 0.907−0.995], p = 0.030. A strong association between *BRAF* mutations and lower AR levels was found both in the overall population (t-test; p = 0.0005) and in *KRAS* wt subgroup (t-test; p = 0.0023). In the subgroup of 40 (47%) *KRAS* and *BRAF* wt patients AR expression did not predict RR (OR: 0.969 [95%CI: 0.898−1.046], p = 0.422) nor PFS (HR: 0.983 [95%CI: 0.948−1.019], p = 0.345) nor OS (HR: 0.968 [95%CI: 0.924−1.014], p = 0.175).
In *KRAS* wt subgroup, at the multivariate analysis *BRAF* mutation retained its predictive value in terms of both PFS (HR: 2.577 [95%CI: 1.103−6.022], p = 0.029) and OS (HR: 3.472 [95%CI: 1.417−8.506], p = 0.007), while AR expression did not predict PFS (HR: 0.982 [95%CI: 0.947−1.018], p = 0.320) nor OS (HR: 0.968 [95%CI: 0.924−1.014], p = 0.17).
Conclusions: *KRAS* and *BRAF* mutations are confirmed as predictors of resistance to cetuximab plus irinotecan. The significant association between *BRAF* mutations and lower AR expression suggests that decreasing levels of AR expression may be an epiphenomenon of *BRAF* mutations. Future studies of potential predictors of benefit should take into account their possible overlap.

6114 POSTER

K-ras and B-raf mutation analysis has clinical value in stage III colon carcinoma

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Background: Mutations in the k-ras pathway have been widely studied in metastatic colon carcinoma due to their value as predictive markers of response to anti-epithelial growth factor receptor therapy. However the value of disruption of this pathway in other stages of colon carcinoma remains unknown.
Our aim is to study the clinical value of mutations in the *k-ras* and *b-raf* genes in a well defined and clinically homogeneous group of stage III colon carcinoma patients.
Patients and Methods: 213 patients with stage III disease treated with surgery followed by 5-FU based adjuvant therapy were selected. DNA was isolated from selected areas of paraffin material, after determination of percentage of tumoral cells. K-ras mutations in codons 12 and 13 were determined by sequencing. The V600E mutation in the B-raf gene was studied by real time PCR with specific probes for the mutated and the wild type allele. MSI status was determined by typing the BAT 26 marker which is positive in 99% of MSI positive Caucasian patients.
Results: Median age of the group was 64 years (30−83), median follow up was 47 months (4–133). 56.8% of the patients was male and 52.6% had a right sided tumor. 76.4% of the patients had less than 4 positive lymph nodes at diagnosis and 73.7% had a T_3 tumor. 14% was MSI positive, 19.5% had a mutation in the *b-raf* gene and 35% had a mutation in the *k-ras* gene. Mutations in the *b-raf* and *k-ras* genes were mutually exclusive. There was a significant relationship between B-raf mutation and MSI positive tumors (p < 0.0001) and between B-raf mutation and right sided disease (p < 0.0001). In our group the presence of a mutation in the *k-ras* gene significantly correlated with developing a distant metastasis or local recidive during follow-up (p = 0.009).
In a multivariate survival analysis adjusting for known prognostic factors like lymph node status, T status, age, gender, tumor location, MSI, B-raf and K-ras mutations; the V600E mutation in B-raf was an independent factor significantly predicting a worse overall survival (p = 0.006 95% CI (0.21−0.78)). K-ras mutations was an independent factor predicting shorter disease free survival (p = 0.028 95% CI (0.34−0.94)).
Conclusion: We conclude that mutation analysis of the K-ras pathway is a useful clinical tool to predict overall survival and disease free survival in stage III colon carcinoma patients.

6115 POSTER

VEGF gene polymorphisms in the prediction of benefit from first-line FOLFIRI plus bevacizumab (BV) in metastatic colorectal cancer (mCRC) patients (pts)

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Background: Addition of BV to first-line irinotecan plus 5FU improves PFS and OS of mCRC pts. Meanwhile, the anti-VEGF causes specific toxicities and increases costs of treatment. At the same time, not all pts derive an equal benefit from the VEGF inhibitor. So far, molecular predictors of BV efficacy have not yet been identified. Specific *VEGF* polymorphisms may affect gene transcription, thus indirectly influencing efficacy of BV.
Materials and Methods: Peripheral blood samples for genomic DNA extraction were collected from consecutive mCRC pts receiving FOLFIRI plus BV as first-line treatment (BV-group). *VEGF* −2578A/C, −460C/T, +405C/G, +936C/T polymorphisms were analysed by means of PCR-RFLP. One-hundred-seven pts, treated with FOLFIRI alone, served as historical control group.
Results: One-hundred-eleven pts were included in the BV-group. M/F = 57/54, median age = 63 (34−82), Köhne score (low/intermediate/high/data missing) = 57/39/12/3. Sixty-nine out of 111 pts achieved response (RR = 62%). Median PFS (mPFS) and median OS (mOS) were 10.2 and 22.2 months, respectively. *VEGF* −460C/C, C/T and T/T allelic variants were found in 20%, 54% and 26% of pts, respectively. −460 T allele demonstrated shorter PFS and OS with an additive effect of each T allele (PFS: HR = 2.65, [1.49−6.62], p = 0.003; OS: 2.47, [0.91−7.66], p = 0.074). −460C/C pts achieved significantly longer PFS and OS in comparison to pts carrying at least one T allele (mPFS: 12.8 vs 9.8 months; HR = 0.48 [0.28−0.85], p = 0.012; mOS: 27.3 vs 20.5 months; HR = 0.38 [0.19−0.94], p = 0.034). In the control group mPFS and mOS were 8.2 and 20.6 months; −460C/C, C/T and T/T variants were found in 23%, 52% and 25% of pts, respectively; there was no significant association with PFS or OS. Other investigated polymorphisms did not affect outcome neither in BV-group nor in the control group.
Conclusions: At our knowledge this is the first report of a pharmacogenetic determinant of improved PFS and OS for mCRC pts treated with first-line BV-containing therapy. The observation that *VEGF* −460C/T variants did not influence the outcome in the control group led to hypothesize a predictive other than a prognostic role for such genetic signature. These preliminary data deserve investigation in prospective, randomized, validating trials.

6116 POSTER

Epidermal growth factor receptor (EGFR) expression in stage II-III colon carcinoma (CC) – nine years of follow-up

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Background: Epidermal growth factor receptor (EGFR) is a protoncogen that is found overexpressed in colorectal carcinomas and it correlates with a worse prognosis. The aim was to describe EGFR overexpression patterns in non-metastatic CC and to correlate these data with follow-up.
Methods: We analyzed a series of 194 CC. Inclusion criteria were: a) resected primary adenocarcinoma; b) curative surgery; c) pT3 N0−2 M0 without progression during the first 6 months post surgery; d) minimum follow-up over 8 years. EGFR overexpression was analyzed by immunohistochemistry (IHC) using the Dako PharmaDx kit (Glostrup, Denmark). As positive control the Dako slides and a bloc cell of A431-AAM cells were used. Presence of cytoplasmic and membrane patterns (intensity 1(+), 2(+) and 3(+)) were evaluated as well as the percentage of positive cells. Statistical analysis: association between qualitative variables was analyzed by Fisher's exact test. Disease-free and overall survival distributions were estimated by the Kaplan-Meier method and were analyzed with the log rank test. All *P* values are from two-sided statistical tests.