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Prognostic role of prominent tumour-infiltrating lymphocytes in early stage gastric carcinoma

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Background: The degree of lymphocytes infiltration is a significant determinant of outcome for a variety of malignancies including non Hodgkin's lymphoma, oesophageal carcinoma, malignant melanoma, colorectal carcinoma and breast cancer. Pathologists have for a long time recognised that tumour prognosis is closely correlated with several morphological features including histological type, TILs, tumour associated eosinophils and mast cell. Gastric cancer could be associated with lymphocytic infiltrate, although the functional role and prognostic significance of this infiltrate is unknown.
Materials and Methods: Patients: Between 1993 and 2004, 204 patients underwent a R0 gastric resection for T1−T2 N0. 55 of these patients (31 men and 24 women with a mean age of 62.82±11.8) were analysed. Correlation between free disease survival and clinical (age, sex), and pathological features (tumour site and diameter, Laurén, Bormann and WHO classification, vascular and lymphatic invasion, pTNM) were analysed. Histopathological examinations – All surgical specimens stained with haematoxylin and eosin (H&E). Microscopic examination included histological differentiation of tumour, assessment of invasion, identification of presence of cancer cells at the surgical margin and IEL, PLT and CRL infiltrating lymphocytes. Statistical analysis – Software SPSS 11.0 was used for statistical analysis (SPSS Inc., Chicago, IL, USA). Correlations of clinic pathological features and molecular alterations gastric and disease free survival cancers were analysed using the Cox regression. Overall disease free survival was calculated according to the Kaplan-Meier method, and the log-rank test was used to determine statistical differences between life tables, considering significant values of $p < 0.05$.
Results: Tumour associated mononuclear inflammatory cell, such as lymphocytes communicate with each other by extra cellular signals such as cytokines and their soluble receptors. Several cancer cell lines suggest that they are produced largely by tumour cell. No statistically significant difference was observed in terms of age, sex, site of tumour, diameter, grading, CEA and Ca 19.9 levels, lymphatic and vascular invasion, classification (Lauren, Borrmann WHO). The presence of IEL, PTL and CRL was showed in 26 patients (48.8%), 31 patients (56.8%) and 24 patients (43.2%) respectively. Presence of IEL and CRL strong predicts a better disease free survival. Patients with high levels of IEL and CRL demonstrate a lower rate of relapse ($p = 0.0003$ and $p = 0.005$ respectively). We did not found PLT and CRL in patients with relapse.
Conclusion: At present, there is no reason to expect a single predictive molecular factor to emerge that determines with high sensitivity and specificity that a patient is to expect disease recurrence or will profit from adjuvant therapy, respectively. But this preliminary study suggests that TILs may be useful as predictors of patient survival in surgically treated early stage gastric cancer.

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Acute oxaliplatin neurotoxicity may be related to SK3 polyglutamine tract polymorphism: a translational study

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Background: Antineoplastic agent l-oxaliplatin (l-OHP) presents a unique acute neurotoxicity which is clinically characterized by cold-induced paresthesias, muscle cramps and tightness. At nerve conduction studies, OHP-treated patients shows signs of abnormal nerve hyperexcitability (NHE) that resemble neuromyotonia, a rare autoimmune disease cause by autoantibodies directed against voltage-gated potassium channels (VGKC). Also OHP-related neuro-toxicty is thought to be a channellopathy but there is no agreement about the channel involved, most investigators favouring voltage-gated sodium channels.
SK3 voltage-gated potassium channels are mainly located in the peripheral nervous system and are characterized by a highly polymorphic CAG motif. We hypothesized that SK3 potassium channel dysfunction might be responsible for nerve hyperexcitability in patients treated with oxaliplatin.
Materials and Methods: Patients eligible for an oxaliplatin-containing regimen were enrolled. Detailed neurological examination, nerve conduction studies (NCS) and needle electromyography (EMG) were performed before and after oxaliplatin administration in all patients. Furthermore, a venous blood sample was obtained from each patient in order to perform genetic analysis. Genomic DNA was extracted from patients' leukocytes and PCR-mediated amplification of the second polyglutamine CAG tract of SK3 gene was carried out; PCR products were analyzed on polyacrylamide gel stained with Ethidium Bromide. DNA samples were extracted from polyacrylamide gel and genotyped with an ABI PRISM analyzer.
Results: We evaluated 13 patients (9M, 4F); mean age was 59 years. According to neurophysiologic data it was possible to divide patients (pts) into three groups: G0 (no symptoms or signs of NHE), 4 patients; G1 (cold induced paresthesias-mild NHE), 5 pts; G2 (muscle cramps; burning paresthesias-severe NHE) 4 pts. Genetic analysis showed different alleles ranging from 13 to 19 repeats. In particular, all patients carrying a 13−14 repeats allele experienced severe acute toxicicy (G2 group). Patients belonging to G1 group carried alleles ranging between 15 and 17 repeats, with exception of a single patient carrying a 14 repeats allele. Almost all patients with no acute toxicity (75%) had a 18−19 repeats allele.
Conclusions: Acute and reversible NHE observed in some patients treated with l-OHP might be produced either by an increased sodium conductance or by a decreased activity of potassium channels. The high percentage of a short polyglutamine tract that we found in the G2 group, induces us to think that the polymorphism at CAG locus of SK3 may be responsible for l-OHP toxicity, rather than a disfunction of voltage-gated sodium channels. Accrual of patients is ongoing.

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Breast cancer detection in mammography screening has independent influence on survival when cancer size and biological subtype are accounted for

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Background: A few studies suggest that detection of breast cancer in mammography screening is associated with favourable survival even when the generally smaller size of screen-detected cancers is accounted for. We examined whether the frequency of gene expression-derived breast cancer subtypes differs between cancers detected in mammography screening and outside of screening.
Material and Methods: Unilateral, invasive breast cancers without distant metastases (M0) at the time of the diagnosis and diagnosed in Finland in 1991 to 1992 were reclassified into 5 subtypes based on immunohistochemistry/chromogenic in situ hybridization as follows: luminal A (ER+ and/or PR+, HER2−), luminal B (ER+ and/or PR+, HER2+), basal-like (ER−, PR−, HER2−, cytokeratin 5 positive, and/or HER1+), HER2+/ER− (ER−, PR−, and HER2+), and unclassified (negative for all 5 markers). The median follow-up time was 9.5 years.
Results: The required biomarkers and clinical data were available for 1,491 (75%) of the 2,001 cases that filled the study eligibility criteria. Of the 5 subtypes, the luminal A subtype was associated with the best distant disease-free survival and the HER2+/ER− subtype with the worst ($P < 0.0001$, log-rank test). Screen-detected cancers were more often of the luminal A subtype than cancers detected outside of screening (72% vs. 64%, respectively, $P = 0.02$), and they were less often of the HER2+/ER− subtype (5% vs. 10%, $P = 0.02$). Cancer detection outside of screening was an independent unfavourable prognostic factor (HR 1.89, 95% CI 1.21−2.95, $P = 0.0005$) together with high histological grade, a large number of metastatic axillary nodes, large primary tumour size, young age at cancer detection, and unfavourable cancer subtype in a multivariate analysis.
Conclusions: Breast cancers detected in mammography screening are less often of the HER2+/ER− type than cancers detected outside of screening. However, cancer detection in mammography screening had independent favourable influence on survival in a multivariate analysis that contained both cancer subtype and size. These findings suggest that neither cancer size nor subtype fully explains the influence of the mode of cancer detection on survival.