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Clinical characteristics, treatment outcome, and prognosis of Philadelphia chromosome-positive adult acute lymphoblastic leukemia

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Background: Philadelphia chromosome (Ph)-positive acute lymphoblastic leukemia (ALL) is a common cytogenetic abnormality in adult ALL and found in 15% to 30% of patients. It is associated with poor outcome both in children & adults. No therapeutic approach has had substantial impact on its unfavorable course This preliminary study is reported to define the frequency of prevalence of the BCR-ABL fusion subtypes in our ALL patients by reverse transcription-PCR (RT-PCR) and to ascertain the prognostic significance of t9:22translocation along with other characteristics.
Patients and Methods: Sixty-five adult ALL patients treated at our center between 2004 and 2005 comprised the study group. The diagnosis of patients was based on typical morphological criteria of marrow aspirate and biopsy specimens. ALL patients were treated with induction regimen consisting of a combination of vincristine, prednisone, daunorubicin, L-asparginase and cyclophosphomide followed by courses of intensification and CNS prophylaxis and consolidation I, reinduction, consolidation II, maintenance, and central nervous system (CNS) prophylaxis.
Results: Among the patients included in this study, Ph-positive ALL was present in 16 of 65 patients (25%). The number of patients within 3 age groups (<20 years, 20−50 years, >50 years) differed significantly between BCR-ABL+ and BCR-ABL− patients (P = 0.001). The median age was significantly higher in the BCR-ABL+ group (30 versus 15 years; P = 0.0001). BCR-ABL+ patients were also characterized by higher median white blood cell (WBC) counts (180000/μL versus 23000/μL P = 0.0001). A complete remission (CR) after induction therapy was achieved in 30 of 49 (61%) BCR-ABL− patients and 6 of 16 (38%) BCR-ABL+ patients (P = 0.001). Only 10% the BCR-ABL− patients achieved complete continued remission while none of the BCR-ABL+ patients maintained a CR further. The presence of a BCR-ABL fusion predicted (P = 0.0001) a lower survival. The estimates of event-free survival and overall survival two years after diagnosis in the combined study group were 20 percent and 30 percent, respectively. Age, initial leukocyte count, were found to have a significant effect on the outcome of treatment. The probability of overall survival at 2 years after diagnosis was 0.30 (±0.03 SE) in BCR-ABL− (n = 49; median survival, 360 days) versus 0.15 (±0.03 SE) in BCR-ABL+ patients (n = 16; median survival, 240 days; P = 0.0001). The DFS of BCR-ABL+ patients remains markedly low (with CALGB protocol at 2 years, 0.08±0.03 SE). Multivariate analysis confirmed WBC count and BCR-ABL result as an independent prognostic factors.
Conclusion: This study emphasizes that BCR-ABL gene fusion is an independent prognostic factor in ALL patients. Identification of this genetic entity in adult ALL at diagnosis is crucial for understanding the nature of adult acute lymphoblastic leukaemia and for deciding optimal treatment

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Real time PCR biomarker analysis reveals the molecular mechanisms involved in bladder cancer progression to complement classical staging for the assessment of prognosis and treatment selection

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Background: Management of bladder cancer patients is based on hystopathological characterization. Still, the appearance of early recurrences is hard to predict and causes great suffering and most of the deaths. We aimed to study the potential impact of incorporating gene expression level analysis methods to improve the success of clinical decisions.
Materials and Methods: Good quality total RNA from a total number of frozen biopsies from 97 patients, including 77 tumors and 40 biopsies from macroscopically unaffected bladder, were analysed by means of real time RT-PCR. Gene expression levels (RE) of EGFR, VEGF-A, CDH-1, TSP-1, HURP, Survivin, MMP9, IL-18 and COL1A1, using RPL13′s expression level for normalisation, were determined. Using SPSS v13.0 software non-parametric statistical analysis tests (Kruskal-Wallis, Mann-Whitney and Wilcoxon) and ROC curve analyses were run, considering tumor's histological stage, grade and extension, and the appearance of early postsurgical recurrences.
Results: Among the analysed bladder tumor biomarkers, EGFR and CDH-1 were most selective for the identification of superficial bladder tumors (Ta-T1), while infiltrating tumores were characterised by the overexpression uf HURP, SURV and TSP-1 (T2-T3). MMP-9 was overexpressed in infiltrating tumors compared to superfitial ones (p 0.034) and in large (>3 cm) compared to smaller or multiple tumors (p 0.001). Antiangiogenic TSP-1 levels were higher in Ta compared to T1 and in G1 compared to G2-G3 tumors. EGFR was overexpressed in the unaffected bladder of a high proportion of infiltrating tumor patients (27%). COL1A1 expression characterised unaffected bladder biopsies, specially in T1 compared to Ta patients (p 0.048). Fibrosis related proinflammatory mechanisms were assessed through the IL-18 expression levels, observing higher IL-18 levels in the unaffected bladder of patients with multi-focal tumors (p 0.045). None of the analysed biomarkers on its own was able to predict early postsurgical recurrences in the patient population during the two-year follow-up period considered.
Conclusions: The identification of different overexpressed genes in hystopathodolgically different bladder tumors indicates that specific molecular mechanisms contribute to cancer progression in these patients. Thus, different therapeutic strategies should be considered taking into account the gene expression profile that characterizes each patient's tumor and its microenvironment.

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Stromal and epithelial interactions in three dimensional models of ovarian cancer

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Epithelial ovarian cancer has the highest mortality rate among gynaecologic malignancies in the Western World. The development of novel epithelial ovarian cancer therapies depends on appropriate experimental models of disease pathogenesis. It is widely accepted that the ovarian surface epithelium (OSE) is the precursor tissue of ovarian invasive cancers. However, the stromal component of both normal ovaries and ovarian tumours plays an important role in directing proliferative and functional changes in the epithelium. Stromal cells can regulate the epithelium through the production of soluble growth stimulatory and/or inhibitory factors; and components of the extracellular matrix such as collagens, fibronectin and laminin can also act as signalling molecules for epithelial cells. We have established and characterised the molecular features of primary cultures of epithelial and stromal cells from different combinations of malignant and benign ovarian cancers, and normal ovaries. Cultures have been set-up as three-dimensional models using the Rotary Cell Culture System (RCCS), which mimics in vivo conditions of cell growth more closely than standard 2D cultures. The principle hypothesis is, that the interactions between the stromal and epithelial component of primary ovarian cancers is critical to the maintenance of the tumour microenvironment and ultimately the ability of ovarian cancers to metastasise. If this is true, then it might be anticipated that transformed stromal cells will promote transformation of normal/benign epithelial cells when co-cultured and/or that normal/benign stromal cells will suppress the malignant phenotype of neoplastic epithelial cells. Therefore, we assessed the phenotypic effects of different stromal and epithelial components, including growth properties, morphology and neoplasia. We have found that tumour associated stroma promote the growth of epithelial ovarian cells in vitro. This effect was not observed when we co-cultured epithelial ovarian cells with stromal cell lines derived from benign ovarian tumours or with normal skin fibroblasts. The results of these studies will be presented. In the future, we plan to characterise molecular markers associated with stromal-epithelial cell interactions. This might lead to the discovery of novel screening markers for the detection of early stage disease and/or new therapeutic markers.