can be evaluated on clinical and histomorphologic grounds with contribution of immunoprofile and molecular profile (WHO 2001).

Design: Few studies used immunohistochemical expression detection for stratification of DLBCL, Barranas et al.(2002), Colomo et al. (2003), Linderoth et al. (2003), McClintock et al. (2003). Two major patterns of gene expression by gene array technology have been proposed, Alizadeh et al. (2000), Rosenwald et al. (2002), for dividing into prognostically significant subgroups in germinal centre (GC) a post-germinal centre (post-GC) DLBCL.

First publication discribing NFkappaB is mentioned in 1986 (Sen et al) and comprises family of transcription factors with important role in cell proliferation, antiapoptotic function and differentiation. NFkappaB signaling pathway is activated by numerous stimuli e.g. bacteria and viruses and is referred to as a central mediator of the immune response. NFkappaB signaling pathway regulates survival of normal and malignant B-cells by controlling the expression of cell death regulatory genes (Karin et al. 2002). Nuclear localization of NFkappaB leads to binding to the promoters of target genes, Li et al. (2002).

Summary: The sorting in GC and post-GC DLBCL group was used according the immunoprofile as decteted in GC and post-GC B-cells. CD10 is surface antigen that shows positive expression in non-neoplastic GC derived B-cells. Bcl6 is proposed protooncogeneic factor and shows nuclear localised positive expression in GC derived B-cells. MUM1 shows nuclear localised positive expression in post-GC B-cells. The GC group was signed if detected positive expression of CD10 and BCL6 and negative expression of MUM1. The post-GC group was signed if detected positive expression of MUM1 and negative expression of CD10 and BCL6.

Inactive NFkappaB heterodimers (c-REL/RELA, NFkappaB p50/p52, p65/RELA) reside in the cytoplasm, complexed with an inhibitor of IkappaB. The phosphorylation of IkappaB by IkappaK kinase results in the inhibitor`s dissociation from cytoplasmic NFkappaB heterodimer. Phosphorylated IkapaB is degraded via the proteasome. Free NFkappaB heterodimer translocates to the nucleus and induces the transcription of target genes. In our file of DLBCL we evaluated expression of NFkappaB (p50, p52, p65) and in some of cases in post-GC DLBCL group we detected it´s nuclear localisation.

Conclusion: Prognostic and predictive stratification of DLBCL in the group of post-GC DLBCL could be proposed to refine according to expression of NFkappaB family and also according to new available target of therapy, inhibitor of proteasome complex (bortezomib).

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Mutations in the receptor tyrosine kinases in gastrointestinal stromal tumours from Russian patients

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BACKGROUND: Gastrointestinal stromal tumours (GISTs) are often show constitutive activation of either the KIT or PDGFRα receptor tyrosine kinases because of gain-of-function mutation. Aim of the study was to analyze KIT or PDGFRα mutations in GISTs from Russian patients and estimate their prognostic value.

METHODS: We have analyzed 90 DNA obtained from paraffin sections of GISTs in PCR with primers to KIT (exons 9, 11, 13, 17) and PDGRFA (exons 12, 14 and 18) followed with direct sequencing.

RESULTS: 96% of GISTs were CD117 positive. Seventy percents of GISTs harbor KIT mutations in exon 11, most of them were in-frame deletions or substitutions in the 5'-end of exon 11 in a region of 550-563aa. There was one gastric GIST with the deletion of 550-558aa that started in KIT intron 10 and involved the intron 10-exon 11 boundary. All GISTs with deletions in KIT exon 11 were highly malignant. Besides, 11% of GISTs had duplications of 1-12aa in the 3'-end of KIT exon 11 and were low malignant. These GISTs occurred predominantly in women over age 65. Mutations in KIT exon 9 (duplications of 502-503aa) were found in 27% of intestinal GISTs with aggressive behavior and metastases. Mutations in KIT exons 13 and 17 were found in one case each. PDGRFA mutations in exon 18 were found in 10% of GISTs. Typical substitution D842V was found only in two benign gastric GIST with epithelioid cell morphology, while other GISTs contain deletions, involving 842-846aa. There were wild-type KIT and PDGFRA in 13% of GISTs. We have found the additional mutations in KIT exon 17 (D820V and N822K) in GISTs treated with Gleevec that are associated with the secondary resistance to target therapy.

CONCLUSIONS: We have found some peculiarities in the variety of KIT and PDGFRA mutations in Russian patients, namely, high percent of GISTs with KIT exon 11 duplications, low percent of GISTs with D842V PDGFRA substitution, etc. The obtained results revealed some correlations between the type of KIT or PDGRFA mutation and clinico-pathologic parameters of GIST. They support the suggestion that mutational analysis of GIST is important for predicting GIST prognosis and the efficacy of target therapy.

POSTER SESSION

Oncogenomics

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Breast cancer progression – genomic alterations in a continuum of stages

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Aim: To study the progression of genomic alterations in mammary epithelial cells from dense breast tissue to full blown cancers

Materials and methods: In total 127 breast tissue samples from three different series have been analyzed using 244K Agilent Human Genome CGH Microarrays (Santa Clara, CA). The samples comprise: 21 "normal" breast tissue (dense breast tissue, reduction mammoplasties, and normal tissue from mastectomies), 26 ductal carcinoma in situ (DCIS), and 75 breast carcinomas.

Results: Data analysis has been initiated using Nexus software from BioDiscovery (El Segundo, CA). Several of the "normal" samples show signs of alterations in areas known to be commonly altered in breast tumors. Hierarchical clustering revealed heterogeneity within each group of samples, suggesting further stratification. The "normal" samples clustered together with low aberrant tumor- and DCIS samples, while the highly aberrant tumor- and DCIS samples clustered together. Significance Testing for Aberrant Copy number (STAC) was applied to reveal common alterations within each group. Among the "normal" samples 118 genes were found to be in regions having significant frequency p-value ($p<0.05$) and being present in more than 35% of the samples, whereas the number was 105 for the DCIS and 245 for the tumors. Of these genes, 31 were overlapping between all groups. We identified group-specific events defined as at least 0.25-fold copy number change between two of the groups with a p-value < 0.05 using Fisher exact test. Genomic regions were found significantly altered in DCIS and breast cancer samples compared to the "normal" samples harboring 1341 and 2617 genes, respectively. Fewer genes (N=388) were identified in significantly altered regions when comparing breast cancer to DCIS. Enrichment analysis was performed to identify biological processes of significance.

Conclusion: Preliminary analyses reveal heterogeneity within each group and frequency of aberrations appears proportionally related to disease stage. Some genomic regions were found significantly changed in all groups. Most of these regions correspond to frequently observed copy number variations (CNVs) and might be candidate hotspots for early events of genomic rearrangements towards breast cancer development. More samples will be included and further stratification will be necessary to identify possibly important events that initiate and drive breast cancer carcinogenesis.

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High frequency of copy neutral LOH in MUTYH-associated polyposis carcinomas

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Genetic instability is known to drive colorectal carcinogenesis. Generally, a distinction is made between two types of genetic instability: chromosomal instability (CIN) and microsatellite instability (MIN or MSI). Most CIN tumours are aneuploid, whereas MSI tumours are considered near-diploid. However, for MUTYH-associated polyposis (MAP) the genetic instability involved in the carcinogenesis remains unclear, as both aneuploid adenomas and near-diploid carcinomas have been reported. Remarkably, our analysis of 26 MAP carcinomas, using SNP arrays and flow sorting, showed that these tumours are often near-diploid (52%) and mainly contain