THE ROLE OF TOPOISOMERASE II-α (TOPO IIA) AS A PREDICTIVE FACTOR FOR RESPONSE TO NEOADJUVANT ANTHRACYCLINES BASED CHEMOTHERAPY IN LOCALLY ADVANCED BREAST CANCER

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Introduction Topoisomerase II-α is a molecular target of anthracyclines; several studies have suggested that topoisomerase II-α expression is related to response to anthracycline treatment. The objective of this study was to evaluate if topoisomerase II-α overexpression predicts response to anthracycline treatment in locally advanced breast cancer patients.

Material and methods This prospective study included 50 patients with primary non metastatic locally advanced breast cancer according to American Joint Committee For Cancer Staging(T3-4;N0-3)were treated between (January 2012 and January 2012) at Clinical Oncology Department, Tanta University Hospital.

Topoisomerase II-α, HER2, oestrogen receptor (ER), progesterone receptor (PR) expression and Ki-67 were evaluated by immunohistochemistry in formalin-fixed, paraffin-embedded breast tumours from 50 patients presenting with locally advanced breast cancer.

Results and discussions Tumours from 50 patients, 45 (90%) showed topoisomerase II-α overexpression, patients 34 (68%) for ER positive, 32 (64%) for PR positive and 16 (32%) for HER2 overexpression and 12 (32%) for high Ki 67.

Significant correlation between clinical and pathological response with topo IIA, HER2 and Ki-67. p value (≤0.001), (0.005) and (0.015) respectively.

Conclusion Our data support a correlation between topoisomerase II-α, HER2, hormonal receptor negative and high Ki-67. p value (≤0.001), (0.005) and (0.015) respectively.

1-Responders:
v Clinical (CR): 3 patients had co-expression of topo II and HER2, hormonal receptor negative and high Ki-67.
v Clinical(PR):43 patients majority of them had topo IIA overexpression. fig9(10)

2-Non responders:
4 (8%) patients all had negative (TOPOII/HER2), low Ki-67 and 2 had hormonal receptor positive and another 2 had hormonal receptor negative.

Conclusion Our data support a correlation between topoisomerase II-α expression in locally advanced breast cancer patients and improved clinical benefit with neoadjuvant anthracyclines based therapy.

ROLE OF PROMOTER HYPERMETHYLATION OF HOCT1 GENE (SLC22A1) IN RESPONSE TO IMATINIB OF CHRONIC MYELOID LEUKAEMIA PATIENTS

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Introduction hOCT1 (Human Organic Cation Transporter 1), solute carrier transporter of SLC22 gene family,mediates influx of imatinib into cells.It is seen that intracellular imatinib uptake correlates with hOCT1 expression and may alter clinical outcome in CML.DNA methylation in promoter associated CpG islands is a powerful mechanism of gene silencing.Role of promoter hypermethylation of hOCT1 gene in CML and its effect on response to treatment with imatinib has not been studied much.

Material and methods 30 newly diagnosed CML patients aged 18 to 80 years were included in the study before initiation of imatinib.30 healthy volunteers participated as controls.Patients were followed up after initiation of imatinib for 6 to 12 months,haematological and molecular response were assessed.

hOCT1 gene expression was studied by Real Time quantitative PCR.Promoter Methylation of hOCT1 gene was studied by Methylation Specific PCR.

Results and discussions Cases were divided into 2 groups, high expression(n=15) and low expression(n=15) (median fold change=5.6).Median time to achieve complete haematological response(CHR) in high expression group was 1.93+/-0.62 months, in low expression group was 2.67+/-1.06 months (p=0.046).All 15 cases with high expression had optimal molecular response. In low expression group,out of 15,2 had optimal molecular response,6 failure,7 warning.(p=0.000) Methylation was seen in 83.33%of CML cases whereas in only 23.33%of controls.(p=0.001)Methylation was observed in all the 15 patients(100%) with low expression whereas amongst the high expression group,10 out of 15 patients(66.66%)were methylation positive.(p=0.042) No significant association was seen between methylation status and achievement of CHR or optimal molecular response to imatinib.

Conclusion High hOCT1 gene expression is significantly associated with achievement of complete haematological and optimal molecular response to imatinib.Promoter hypermethylation of hOCT1 gene leads to silencing of gene expression.

HOCT1 GENE POLYMORPHISM M420DEL IS ASSOCIATED WITH DECREASED RESPONSE TO IMATINIB IN CML PATIENTS AND AMP; ITS EFFECT IS COUNTERACTED BY M408V POLYMORPHISM

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Introduction Human organic cation transporter1 (bOCT1, SLC22A1), an influx transporter,is responsible for the uptake of Imatinib into chronic myeloid leukaemia (CML)cells. Some patients fail to achieve optimal molecular response to Imatinib, defined as major molecular response (MMR) i.e. BCR-ABL 1≤0.1% within 12 months of therapy. Variation in clinical response to Imatinib has been observed with two nonsynonymous SNPs in bOCT1 gene, namely M420del and M408V in some populations.

Material and methods 30 newly diagnosed BCR-ABL positive CML patients in chronic phase,and 30 healthy control subjects, all ethnic Indians, were recruited in the study. M420del and M408V SNPs were examined by allele specific PCR(AS-PCR) in DNA from PBMCs.After initiation of imatinib therapy, haematological response was monitored at regular intervals, and molecular response (BCR-ABL1/ABL1 ratio) assessed after 6 or 12 months.
Results and discussions Minor allele frequencies for M420del were 0.18 and 0.1 in CML patients and controls; for M408V 0.4 and 0.27 respectively, closely paralleling those reported in western population.

No significant association between different genotypes of M420del and M408V was observed with either time to achieve complete haematological response (CHR) (p=0.341 for both SNPs), or presence of optimal/sub-optimal molecular responses (p=0.125, 0.629 for M420del and M408V respectively).

To analyse the combined effect of these two SNPs, CML cases were divided into 4 groups. Patients with mutant (homo/heterozygous) M420del and wild type homozygous M408V, failed to achieve an optimal molecular response to imatinib, unlike those with mutant genotypes (homo/heterozygous) for both SNPs (p=0.02).

Conclusion Mutant M420del allele may be linked to poor outcome of imatinib treatment in CML, however simultaneous presence of mutant M408V allele appears to circumvent this effect. These SNPs in hOCT1 gene occur at reasonable frequencies in Indian population, to be of clinical interest as predictors of response to imatinib in CML.

PO-472 CHEMOTHERAPY RESISTANCE-ASSOCIATED EPITHELIAL TO ENDOTHELIAL TRANSITION IN GASTRIC CANCER

Introduction Gastric cancer (GC) is the fifth most common cancer worldwide and the third leading cause of cancer-related deaths. To date, gastrectomy and chemotherapy are the only therapeutic options, but drug resistance is the main cause for treatment failure.

Vasculogenic mimicry (VM) is a new model of neovascularization in aggressive tumours and has been correlated with poor prognosis in GC patients.

Our group has developed chemotherapy-resistant GC cells using the Caucasian adenocarcinoma cell line AGS and three drugs among the most used in clinic (5-fluorouracil, cisplatin and paclitaxel) henceforward denominated 5FU, CISr, TAXr.

Our study has highlighted phenotypical differences among chemosensitive and chemo-resistant cell lines such as acquisition of stem-like phenotype and increased capacity to form vessels.

Material and methods Establishment of AGS resistant cell lines exposing cells to increasing dilution of drugs for over 9 months up to dilutions higher than IC50 values initially verified on AGS cells through MTT analysis.

Quantitative RT-PCR, flow cytometry and western blot analysis for stemness and VM markers.

Vasculogenic mimicry assay

Results and discussions AGS cells acquired chemoresistance as indicated by the increase of IC50 values in drug-treated cells with respect to AGS. Furthermore, MTT assay highlighted that there is not cross-resistance among 5FU, CISr and TAXr. Supportive data is that cells are MDR1 negative.

Resistant cells showed an upregulation of Yamanaka factors either in qPCR and flow cytometry analysis, and particularly interesting is ALDH overexpression in 5FU.

TWIST upregulation suggested the investigation of VM which resulted particularly enhanced in 5FU cells which demonstrated their ability to form and sustain vessels up to 96 hours in the tube formation assay.

Markers of VM such Laminin γ2 and Ephrin A2 showed an increase in resistant cells and especially in 5FU.

Conclusion One of the most interesting result is that 5FU cells acquire stemness properties and are positive to the tube