Methods: HUVEC cells tubule formation was measured in the presence of amidated gastrin-17 (G17) and glycine-extended gastrin-17 (GlyG17) peptides. HB-EGF gene and protein expressions were measured by qRT-PCR, immunocytochemistry, and Western blotting, and HB-EGF shedding by ELISA. Matrix metalloproteinases were assessed by Western blotting. Microvessel density (MVD) was assessed by immunohistochemistry and serum-amidated gastrin levels by RIA.
Results: HUVEC cells showed increased tubule and node formation in response to G17 which was blockaded by the cholecystokinin-2 receptor (CCK-2R) antagonist, JB95008 and by antiserum to gastrin and HB-EGF. Gastrin peptides increased HB-EGF gene expression/protein secretion in HUVEC and micro-vessel-derived endothelial cells and the levels of MMP-2, MMP-3, and MMP-9. G17 promoted angiogenesis in a chorioallantoic membrane assay, and MVD was significantly elevated in pre-malignant large intestinal tissue from hyper-gastrinaemic $APC^{Min+/-}$ mice. MVD in the normal mucosa surrounding colorectal adenocarcinomas correlated with patient serum gastrin levels and HB-EGF expression.
The extent to which H. pylori to up-regulation of HB-EGF can be attributed to its effect on gastrin was examined. Gastric cells, transfected with either gastrin small interfering RNA or antisense plasmid or the CCK-2R, were cultured for 24 hours with H. pylori(+/−), a CCK-2R antagonist.
H. pylori-induced significantly higher levels of HB-EGF gene expression and ectodomain shedding in the CCK-2R-transfected cells than the vector control which was reversed by the CCK-2R inhibitor. Gastrin down-regulation reduced the effect of the bacteria on HB-EGF gene and protein expression levels. Endogenous gastrin and CCK-2R expression were also found to be significantly up-regulated in all cell lines as a result of exposure to H. pylori. Finally gastrin has been shown along-with VEGF to be a target gene of HIF1a and be up-regulated under hypoxic conditions in vitro.
Conclusions: The above studies confirm the multi-factorial role of gastrin in gasto-intestinal malignancy confirming it as a target for both chemoprophylaxis and established cancers.

Symposium (Tue, 25 Sep, 14:45−16:45)
FECS/ASCO symposium – what have we learnt from pre-surgical medical therapy in breast cancer?

85 INVITED

The role of neoadjuvant therapy

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Experiments on preclinical models have suggested that preoperative introduction of chemotherapy (CT) of endocrine therapy can improve survival by abrogating a post surgical growth spurt and by addressing micrometastatic disease at an earlier stage than when given postoperatively. Clinical trials have not confirmed this hypothesis, although they have demonstrated that neoadjuvant systemic therapy (NST) reduced overall tumor burden, expanded the indications for breast-conserving surgery to patients (pts) with more advanced disease, and provided an in vivo assessment of response that facilitated the safe and effective administration of systemic treatment. NST also provides an improved investigational model, since sequential monitoring with the primary tumor in place offers the opportunity for multiple biopsies to monitor the biological effects of treatment. Large randomized trials have shown preoperative CT to be at least equivalent in disease-free and overall survival to the same CT administered postoperatively. Emerging data suggest, however, that the effects of systemic therapy in general, and NST in particular, vary with different subclasses of breast cancer (BC). The first such observations were based on estrogen receptor (ER). The magnitude of benefit from CT is proportionately more modest for pts with ER+ tumors than for ER− tumors. This is dramatically expressed in preoperative trials, where the pathological complete remission (pCR) rate is four to six-fold higher for ER− than for ER+ BC. Similar variation in pCR rate is observed by grade and histologic type (invasive lobular cancers vs. invasive ductal cancers). Paradoxically, although pCR identifies a group of patients with improved survival compared with patients who do not achieve pCR, patient groups with lower pCR rates (those with ER+ tumors, those with low grade or lobular cancer) have better overall survival than those that tend to have higher pCR rates. This observation emphasizes the importance of understanding the biological heterogeneity of BC. Studies based on gene expression profiling in BC have confirmed the existence of at least three distinct forms of BC: ER+/HER2-, HER2+, and “triple-negative”. These three groups differ by much more than the individual gene (ER or HER2) expression, and their clinical course and responsiveness to different treatments is quite different too. Thus, HER2+ and triple-negative tumors achieve a high pCR rate (40-50%) with standard combinations, while ER+/HER2− tumors do not (pCR rate <10%). Gene profiling also leads to the identification of potential new therapeutic targets. Validation of such novel targets and development of specific therapeutics might be the best legacy of NST.

86 INVITED

Biological lessons from adjuvant therapy

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Neoadjuvant therapy offers a convenient setting to test for predictive factors to drug response. Primary tumours in general are suitable for tissue sampling and tumour response evaluation. In addition, such studies allow us to draw important conclusion from a limited number of patients. However, while a complete response on primary chemotherapy has been found associated with long term outcome, patients achieving a complete response may still develop distant metastasis. Thus, micro-metastasis may harbour resistant cells not easily detectable in the primary tumour. Further, not every patients progressing locally on therapy are subject to subsequent relapse even in case they are treated with local salvage therapy only. These findings illustrate the complex issue of primary response versus risk of metastases and long-term outcome.
Despite these limitations, neoadjuvant therapy offers an important setting to test for chemoresistance. While success so far has been limited with respect to identify predictive factors validated for clinical use, this is likely to change. Following development of improved methodologies and, in particular, more knowledge about biological parameters to look for, it is likely that such studies may offer unique results in the not-to-far future. With more protocols becoming available and longer patient follow-up, the potential exist to obtain tissue from distant metastasis in patients who subsequently relapse following participation in neoadjuvant trials. Thus, comparing biological parameters of such metastatic deposits to primary tumour biopsies may offer a unique opportunity to identify key biological events involved in a transformation of cells towards resistance.

87 INVITED

Neoadjuvant antiHER2 therapy

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With the success of trastuzumab treatment of HER2 positive metastatic disease, a number of phase II trials were launched evaluating various trastuzumab-chemotherapy combinations in patients with HER2 positive stage II/III breast cancer. These combinations, which utilized trastuzumab in conjunction with agents including paclitaxel, docetaxel, carboplatin, cisplatin, and vinorelbine, demonstrated high response rates and relatively high pathologic complete response rates. A randomized phase II trial from MD Anderson Cancer Center demonstrated a pathologic compete response rate in excess of 50% with a combination of trastuzumab and paclitaxel followed by trastuzuamb with an epirubicin-based regimen. While there are multiple possible explanations for the extraordinarily high pathologic complete response rate in this study, the most intriguing explanation relates to the concurrent use of trastuzumab and an anthracycline. A phase III trial has been designed to evaluate this regimen further.
From a research perspective, preoperative studies represent an ideal opportunity to pose translational questions related to HER2 positive disease. To date, preoperative studies have suggested that neither ER status nor HER2 status change frequently in response to trastuzumab-based therapy. Furthermore, it appears that a brief exposure to trastuzumab does not change proliferation rate, but does induce apoptosis. Preliminary work also suggests that there may be a gene signature associated with trastuzumab resistance.
Three randomized trials will soon be open in BIG, the US Intergroup, and the NSABP to compare trastuzumab and lapatinib combinations in the preoperative setting. Not only will these studies compare pathologic complete responses rates, but more importantly, they will collect and interrogate tissue. In this way, it is hoped that the studies will lead to a more complete understanding of factors that predict and/or mediate sensitivity and resistance to HER2-directed therapy.
Recent results and planned trials will be reviewed.

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Biological lessons from pre-surgical endocrine therapy

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Pre-surgical medical studies allow a unique opportunity to integrate clinical and biological observations as a result of the taking of sequential biopsies