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212 Invited

Targeting DNA repair deficiency

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Epithelial carcinomas are in general diseases occurring as a result of the acquisition of and selection for multiple mutations in a parental somatic cell clone in the tissues of the primary site. In the last two decades the role of genome caretakers, which function in key areas of the DNA damage response, have been recognized as important tumour suppressor genes. Inactivating mutations in these genes occur as germline and/or as somatic mutations. In either event, loss of function in a tumour cell pre-cursor clone leads to accelerated mutation acquisition and underpins the etiology of the tumour. As an understanding of the complex network that is the DNA damage response matures additional roles for signaling pathways, already recognized to be central to the establishment of the cancer phenotype, as controllers of DNA repair are being discovered. This has relevance to identification of wider populations susceptible to approaches that target DNA repair deficiency. Many established cancer chemotherapeutics exert their effect by creating DNA damage that has some selectivity for tumour cells. How populations of patients respond to these agents at common tumour primary sites have been explored in recent trials. The nature of some of these analyses will be explored in epithelial cancers and breast cancers specifically. More recently the development of targeted therapies, such as PARP inhibitors, that can target deficiencies in DNA repair have been described. The results of the first trials that explore these approaches, based on the concept of synthetic lethality, are emerging and will be reviewed. In contrast to the role of some tumour suppressor genes and oncogenes, continued loss of function of genome caretakers may not confer continuing selective tumour survival advantage after the establishment of the fully malignant phenotype. Indeed a selective pressure may exist for regain of DNA repair functions during DNA damaging therapy. The rationale, pre-clinical and clinical evidence for these potential resistance mechanisms will be reviewed.

213 Proffered paper oral

Duplication of chromosome 17 CEP predicts for anthracycline benefit: evidence from an international meta-analysis of 4 adjuvant breast cancer trials for the HER2/TOP2A meta-analysis study group

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Background: Evidence for *HER2*/*TOP2A* as predictive biomarkers of anthracycline response is conflicting. An interim meta-analysis (Di Leo *et al Cancer Res*;69:99S) suggested a weak, but statistically significant, association between *TOP2A* and anthracycline benefit. We have previously shown that duplication of chromosome 17 alpha satellite (CEP17) predicts sensitivity to anthracyclines [1,2]. We have now performed a retrospective meta-analysis, incorporating data from 4 trials (BR9601, *NEAT,* MA.5 and the Belgian study), to test the hypothesis that CEP17 duplication is a predictive biomarker for anthracycline benefit and provide a unifying hypothesis for previous conflicting data.

Methods: FISH was performed in 2 laboratories (Bartlett for BR9601/NEAT & Belgian studies & O'Malley for MA5). ER/PgR (IHC) etc were collected from trial Case Report Forms. BR9601/NEAT & Belgian study tumors were scored counting all cells with a minimum of one CEP17 signal/cell: in MA.5 a minimum of 2 CEP17 signals were required for cells to be scored. These methodological differences did not affect HER2/CEP17 ratios but necessitated different definitions for CEP17 duplication defined as >1.86 observed copies/cell for BR9601, NEAT and Belgian [3] and >2.25 for MA.5 [4].

Results: FISH was successful in 85% (2531/2975) of cases. CEP17 duplication was detected in 27.5% of tumors (BR9601=37.6%, NEAT=20.0%, MA5=40.2% & Belgian = 28.5%) and was associated with poorer OS & RFS (HR 1.27, 95% CI 0.10–1.47, p = 0.018 & HR 1.25 95% CI 1.09–1.43 p = 0.011, respectively).

A significant treatment by marker interaction (CEP17) was observed in a meta-analysis of all data (2531 cases) as univariate ($p < 0.005$) & multivariate regression analyses (adjusted for treatment, grade, size, ER, nodes CEP17, CEP17-by-treatment & HER2) Recurrence free survival (RFS) hazard ratio (HR) was 1.67 (95% CI 1.25–2.22, p = 0.0006) and overall survival (OS) HR was 1.63 (95% CI 1.18–2.22, p = 0.003). In the two largest studies, NEAT (n = 1462) and MA5 (n = 622), this treatment by marker interaction (CEP17) was significant for RFS ($p < 0.05$) and in all other analyses non-significant trends for OS & RFS were seen. (Trial specific HRs with 95% CIs RFS: 0.73 (0.32–1.79), 0.56 (0.34–0.93), 0.62 (0.39–0.98) & 0.59 (0.15–2.33), OS: 0.74 (0.30–1.85), 0.61 (0.36–1.04), 0.60 (0.35–1.01) & 0.49 (0.10–2.33); BR9601, NEAT, MA5 & Belgian respectively) analyses. HER2 (all 4 trials) and TOP2A (NEAT/BR9601) did not show any significant interactions.

Conclusions: Meta-analysis of 4 adjuvant breast cancer trials shows a highly significant treatment by marker effect for CEP17 duplication as a predictor of anthracycline benefit for both RFS and OS in univariate and multivariate regression analyses. CEP17 duplication may reflect either chromosomal instability or polyploidy and further analysis will explore the underlying mechanisms for this effect. CEP17 is readily assessed in ISH analysis of HER2 status and may represent a clinically useful biomarker for selection of patients likely to benefit from anthracycline containing chemotherapies.

References

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Thursday, 25 March 2010 15:30–17:00

CLINICAL SCIENCE SYMPOSIUM

Lobular cancer is different

214 Invited

Distinct pathological characteristics of lobular carcinoma

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The recognition and diagnosis of morphological variants is critical to stratifying breast cancer into clinically meaningful subgroups and to develop an understanding of the biological nature and the clinical significance of such entities.

Classic lobular carcinomas (CLC) account for 10% to 15% of all breast cancers. It has a very distinct morphology with small cells growing in single files or small aggregates and with a discohesive pattern. At the molecular level, CLCs show recurrent physical loss of chromosome 16q together with the lack of E-cadherin (CDH1 gene) expression. A number of variants have also been described including alveolar, solid and pleomorphic subtypes.

Pleomorphic lobular carcinomas (PLC) of the breast display histological features associated with classic invasive lobular carcinoma (ILC), yet they also exhibit more conspicuous nuclear atypia and pleomorphism, and an aggressive clinical behaviour. This subtype is rare (~1%) and was first described as a high-grade variant of the classic invasive lobular carcinoma (ILC). There has been some contention amongst pathologist as to whether PLC is indeed a discreet entity, a lobular variant or even a type of high grade IDC. The introduction of E-cadherin immunohistochemical staining into diagnostic practice to help differentiate lobular and ductal carcinomas, together with molecular genetic analysis has added support for PLC being a lobular variant. PLC is now becoming accepted as a clinically important tumour subtype with an aggressive phenotype and a poor prognosis.

Considerable progress has been made in understanding molecular biology using a variety of methodologies including comparative genomic hybridization (CGH), array CGH, expression profiling and sequencing. The morphological and molecular profiles of the classic and variant subtype, in particular the pleomorphic variant will be discussed.

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Special aspects of local treatment for invasive lobular carcinoma

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Infiltrating lobular carcinoma (ILC) is known − as compared to other breast cancer types − for its multicentricity, its more diffuse growth pattern and the