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212 Invited

Targeting DNA repair deficiency

A. Tutt[1]. [1]*King's College London, Breakthrough Breast Cancer Research Unit Research Oncology Guy's Hospital, London, United Kingdom*

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

J.M.S. Bartlett[1], A. Munro[1], F.P. O'Malley[2], H. Earl[3], C.J. Poole[4], F. Cardoso[5], C.J. Twelves[6], K.I. Pritchard[7], D.W. Rea[8], A. Di Leo[9]. [1]*Edinburgh Cancer Research Centre, Pathology, Edinburgh, United Kingdom;* [2]*University of Toronto, Pathology, Toronto, Canada;* [3]*University of Cambridge, Medical Oncology, Cambridge, United Kingdom;* [4]*University of Warwick, Medical Oncology, Warwick, United Kingdom;* [5]*Institut Jules Bordet, Medical Oncology, Brussels, Belgium;* [6]*University of Leeds, Medical Oncology, Leeds, United Kingdom;* [7]*NCIC CTG, Medical Oncology, Toronto, Canada;* [8]*University of Birmingham, Medical Oncology, Birmingham, United Kingdom;* [9]*University di Prato, Medical Oncology, Prato, Italy*

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.

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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

S.R. Lakhani[1], P.T. Simpson[1]. [1]*UQ Centre for Clinical Research, Molecular & Cellular Pathology, Brisbane, Australia*

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.

215 Invited

Special aspects of local treatment for invasive lobular carcinoma

P. Poortmans[1]. [1]*Dr. Bernard Verbeeten Instituut, Radiotherapy, Tilburg, The Netherlands*

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

more difficult radiological visualisation preoperatively. As a consequence, a higher incidence of tumour-positive excision margins after lumpectomy and an increased risk of conversion to mastectomy are noted. This explains why breast conserving therapy (BCT) is selected less commonly for women with ILA, although the treatment results are independent of the histological subtype, as confirmed in the EORTC "boost no-boost trial". In a recent population based study on BCT for ILC including 416 patients, the 5 and 8 years local recurrence risk was 3.5% and 6.4%, respectively, despite margin involvement in 29% of the patients after lumpectomy and still 17% when the re-excision was taken into account. In both the univariate and the multivariate analyses, no influence of the surgical margins on the local recurrence risk was found.

A less commonly known and accepted indication for post mastectomy radiotherapy is the case of ILC, independent of the tumour stage. The combined analysis of the EORTC 10801 and DBCG 82TM trials in early stage breast cancer demonstrated that, for this patient category, the local recurrence rate after mastectomy without radiotherapy was 19% at 10 years, compared to only 10% for patients who were treated with a breast conserving approach (HR 2.7, range 1.2−6.3).

In this era where more attention is drawn to the importance of local control even in patients with metastatic disease, it could also be taken into consideration that patients with lobular carcinomas survive significantly longer than other breast cancer patients, particularly from the time of diagnosis of distant metastases.

So in summary, despite the higher risk of an incomplete tumour excision, patients with early stage lobular cancer do not have a higher local recurrence risk after BCT than patients with ductal cancer and could be offered this treatment even after a (focally) microscopically incomplete tumour excision. For patients after mastectomy, lobular histology should also be considered as a separate prognostic factor in favour of referral for radiotherapy.

216 Invited

Risk for metastases and implications for systemic treatment

V. Cocquyt[1]. [1]*UZ University Hospital Gent, Medical Oncology, Gent, Belgium*

Invasive lobular breast cancer (ILC) comprises approximately 5−15% of breast cancers. It appears to have a distinct biology and a different clinical behaviour than invasive ductal carcinoma (IDC).

Compared with IDC, ILC occurs more frequently in older patients, is larger in size and is more frequently oestrogen receptor and progesterone receptor positive. Moreover, ILC has a lower S-phase fraction, tends to be diploid, and is usually HER-2, p53 and epidermal growth factor receptor negative.

The pattern of metastatic dissemination is different for ILC and IDC. IIC is more likely to metastasize to the peritoneum, gastrointestinal tract and ovaries, whereas the lung, pleura, distant nodes and central nervous system are more frequently involved in IDC.

Despite having a more favourable biological profile, ILC is not associated with a better disease free or overall survival rate. In multivariate analyses, histologic type is not an independent prognostic factor for outcome.

However, there is evidence that the clinical and the pathological response to preoperative chemotherapy (PCT) are lower for ILC compared to IDC. This results in larger residual tumour volumes, more mastectomy rates and more positive resection margins after breast conservative surgery, leading to more "rescue" mastectomies. However, the low chemosensitivity to PCT of ILC can probably be explained by their biological profile, but this does not seem to result in a survival disadvantage. Since tumour downstaging is the main aim of PCT, patients with large ILC are probably not good candidates for PCT. In these patients, preoperative endocrine treatment should be further explored.

Recent data suggest that also in the adjuvant setting, adjuvant endocrine treatment results in better response for ILC compared to IDC. In elderly patients with medical comorbidities, who are poor candidates for cytotoxic chemotherapy, endocrine therapy can be a good alternative to improve patients' outcome with ILC.

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217 Proffered paper oral

Outcome of invasive lobular carcinoma compared to infiltrating ductal carcinoma: a population based study from British Columbia

S. Chia[1], M. Al-Foheidi[1], C. Speers[2], R. Woods[2], H. Kennecke[1]. [1]*BC Cancer Agency, Medical Oncology, Vancouver BC, Canada;* [2]*BC Cancer Agency, Breast Cancer Outcomes Unit, Vancouver BC, Canada*

Background: Lobular carcinoma is the 2nd most common invasive breast cancer histology after ductal carcinoma. Though phenotypically they are different, the two histologies are often treated the same with presumed similar outcomes. We sought to compare the baseline demographics, standard pathologic factors and long term clinical outcomes between lobular and ductal carcinoma from a large population based breast cancer registry.

Methods: A retrospective cohort of referred patients to the BCCA with a diagnosis of stage I-III pure lobular or pure invasive ductal carcinoma from 1989–2000 was identified. Prior or synchronous breast cancers and cases with unknown grade were excluded. Standard demographic and pathologic factors was abstracted from the BCCA Breast Cancer Outcomes Unit database and compared between the two histologies. 10 year outcomes were calculated by Kaplan Meier method, with differences compared by log rank test. Median follow up for the entire cohort was 9.3 years.

Results: A total of 13,203 individual patients meeting identified inclusion criteria were identified: 11,911 invasive ductal and 1,292 invasive lobular cancers. Lobular carcinomas generally had a higher frequency of poor prognostic factors: older age ($\geqslant$70 years old), larger tumour size, and greater frequency of N2 nodal involvement (all $p < 0.001$). However lobular carcinomas also had a higher frequency of better predictive factors; ER+ status and low grade tumours (both $p < 0.001$). There were differences in locoregional treatments and systemic therapies between the groups. No differences were seen at 10 year estimated relapse free survival (76% vs 74%), distant RFS (78% vs 77%), breast cancer specific survival (81% vs 81%) and overall survival (69% vs 70%) between lobular and ductal cancers respectively. Only 10 year locoregional RFS significantly favored lobular cancers (93% vs 89%; $p < 0.001$), though there was also a higher mastectomy rate (55% vs 39%) in this cohort.

Conclusion: Though invasive lobular carcinomas are epidemiologically and phenotypically different from ductal carcinomas, clinical outcomes are comparable between these two common histologies.

218 Proffered paper oral

Preventing reoperation in invasive lobular breast cancer

A. Vazquez Guerrero[1], M. Lallement[1], B. Flipo[1], A. Figl[1], J.C. Machiavello[1], C. Chapellier[2], C. Balu-Maestro[2], F. Ettore[3], I. Birtwistle-Peyrottes[1], I. Raoust[1]. [1]*Centre Antoine Lacassagne, Breast Surgery Unit, Nice, France;* [2]*Centre Antoine Lacassagne, Radiology Unit, Nice, France;* [3]*Centre Antoine Lacassagne, Pathology Unit, Nice, France*

Background: Invasive lobular breast cancer (ILC), the 2nd most common breast malignancy, has an increasing incidence, higher failure rates of breast-conserving surgery (BCS) and higher reoperation rates compared to invasive ductal carcinoma (IDC). The value of MRI and associated ultrasound (US) in the workup of ILC has been established. Can reoperation and recurrence be decreased by implementing a clinical algorithm?

Methods: A clinical algorithm was designed with the purpose of lowering reoperation rates and recurrence. Biopsy-proven ILC patients underwent an MRI to estimate extension and feasibility of BCS. Abnormal MRI findings were followed by an US to confirm suspicious lesions and biopsy of these. Positive findings add up points (table 1). Patients $\leqslant$9 points underwent BCS, those $\geqslant$10 points underwent mastectomy. Consecutive patients were included in a 38 month period since 2006 and compared with 195 historical controls. Indication for reoperation: positive margins. Descriptive statistics and exact Fisher's test for *p.*

Results: Biopsy-proven ILC patients (n = 126) were included; 78 (61.9%) underwent BCS, 48 (38.09%) underwent mastectomy, 7 were reoperated. Reasons included close margins on final pathologic evaluation (n = 5), underestimation during intraoperative evaluation (n = 1), and lack of adherence to the clinical algorithm (n = 1). The reoperation rate was lowered to 5.55% compared to 16.92% ($p = 0.0029$). With a mean follow-up of 19.34 months (2−44, SD: 11.61), 4 patients died (2 of advanced second malignancies, 1 catheter-related sepsis in the context of lung cancer, and 1 initially metastatic breast cancer).