195 INVITED

Cell cycle regulation by cyclin-dependent kinases and their inhibitors

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Most human tumors carry mutations that deregulate the G1/S transition of the cell cycle, the process by which quiescent cells initiate their replication. This transition is primarily regulated by the sequential phosphorylation of the Rb family of proteins. Rb phosphorylation is mediated by two classes of cyclin-dependent kinases: Cdk4 and Cdk6, which are regulated by D-type cyclins and Cdk2, which is sequentially regulated by E- and A-type cyclins. In addition, these kinases can be negatively regulated by two families of inhibitory proteins. The INK4 family, which inhibits Cdk4 and Cdk6 by preventing binding of the D-type cyclins, consists of four highly related proteins designated as P16INK4a, P15INK4b, P18INK4c and P19INK4d.. The Cip/Kip family, P21Cip1, P27Kip1 and P57Kip2, blocks Cdk2 by binding to Cdk2-cyclin E/A complexes. Cip/Kip inhibitors also bind to Cdk4/6-cyclin D complexes but do not inhibit their kinase activity. These G1/S regulators are often absent (pRb, P16INK4a, P15INK4b), over-expressed (cyclin D1, cyclin E1, Cdk6) or mutated (Cdk4) in a variety of human tumors such as SCLC (pRb), melanomas (p16INK4a, Cdk4), lymphomas (Cdk6) and breast carcinomas (cyclin D1, cyclin E1). Our laboratory is engaged in studying the role that these proteins play in vivo as well as the mechanism(s) by which they contribute to neoplastic transformation. To this end, we are in the process of generating strains of genetically engineered mice carrying germ line as well as conditional mutations in the genes encoding each of the four cell cycle Cdk's. Here, I will present our results obtained with mice that either lack Cdk4 or express a mutant form (Cdk4R24C) present in human familial melanoma that cannot bind INK4 inhibitors. Cdk4 null mice have a dramatic defect in postnatal proliferation of pancreatic beta cells and testicular Leydig cells. Moreover, these mice are small due to reduced numbers of cells in most organs. Cdk4 (R24C) knock-in mice are slightly larger than their wild type littermates and develop a variety of tumors including those of endocrine origin such as insulinomas, testicular and pituitary tumors. Moreover, these mice are highly susceptible to melanoma development, since most of them develop invasive melanomas upon carcinogenic exposure.

196 INVITED

Microarray expression profiling in breast cancer tailors optimal treatment

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Microarray gene expression profiling combined with advanced bioinformatics is beginning to show its power in delineating disease entities that are otherwise indistinguishable. This refinement in tumor classification allows a more accurate prediction of outcome of disease for patients that present with the same stage of disease based on conventional clinical and histopathological criteria. Gene activities determining the biological behaviour of the tumour may indeed be more likely to reflect the aggressiveness of the tumor than general parameters like tumor size, age of the patient, or even tumor grade. Therefore, the immediate clinical consequences are that treatment schemes can be tailored based on the gene activity patterns of the primary tumor.

We used gene expression profiling with DNA microarrays harboring 25,000 genes on 97 primary breast cancers of young lymph node negative patients to establish and validate a signature, predictive for a short interval to distant metastases. This 'poor prognosis' signature consists of genes involved in cell cycle, invasion and angiogenesis. The prognosis signature is superior to currently available clinical and histo-pathological prognostic factors in predicting outcome of disease (OR = 18 (95% CI 3.3–94), $p < 0.001$, multivariate analysis).

At present, consensus guidelines in the management of breast cancer select up to 90% of lymph node negative young breast cancer patients for adjuvant systemic therapy (e.g., St Gallen). As 70–80% of these patients would have remained disease-free without this adjuvant treatment, these patients are 'overtreated'. Our 'poor prognosis' signature provides a novel strategy to accurately select patients who would benefit from adjuvant systemic therapy and can greatly reduce the number of patients that receive unnecessary treatment.

197 INVITED

How does the clinician integrate rapid advances in molecular biology into patient management

Abstract not received.

Thursday, 21 March 2002 14:45–16:15

EUROPA DONNA SYMPOSIUM

Communication – influences on the doctor/patient relationship

198 INVITED

Can training in communication make doctors' interactions more patient-centred?

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Purpose: To measure the effect of a training course in communication skills on psychosocial attitudes and beliefs and subsequent communication behaviours with patients in consultations.

Subjects and Methods: As part of a large RCT conducted in the UK, 93 clinicians completed a 32-item Physician Psychosocial Belief (PPSB) questionnaire at baseline. They were then randomised to attendance at a 3-day residential communication skills course (N=48) or to a control group (N=45). Three months later both groups completed a further PPSB together with a self-assessment questionnaire recording perceived changes in communication with patients. At both time-points doctors' consultations with 2 consenting clinic patients were videotaped. Communication behaviours were assessed by independent raters using the Medical Interaction Processing System.

Results: Doctors who attended the course showed significantly more positive attitudes and beliefs towards psychosocial issues compared with controls (p=0.002). This improvement was reflected in the analysis of the video-taped recordings of their communication behaviour with patients which was significantly more patient-centred. The course group exhibited more empathy (p=0.042), used fewer leading questions (p=0.024) made more appropriate responses to patient cues (p=0.01) and did more psychosocial probing (p=0.041) than those who did not attend a course. These objective findings concurred with the doctors' self-report of perceived changes in communication style with patients.

Conclusion: The results show that communication skills training interventions that employ behavioural, cognitive and affective components not only increase potentially beneficial and more effective interviewing styles, but can also alter attitudes and beliefs thus increasing the likelihood that patient-centred skills will be employed in clinics.

199 INVITED

The influence of specialist nurses as patient advocates on the doctor/patient relationship

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Specialist breast cancer nurse roles have been developed in the UK since the 1980's. These roles originated in the work of Maguire et al and Watson et al, who investigated the value of specially trained nurses in counselling women following a diagnosis of breast cancer, and in identifying those at high risk of developing psychopathology who might benefit from psychiatric help. Specialist breast care nurses are now seen as integral members of the cancer treatment team, and their role in providing information and support for women undergoing diagnostic investigations and treatment for breast cancer is seen as a core part of breast cancer services. Virtually all breast cancer services in the UK now have specialist breast cancer nurses.

The existence of a significant body of specialist nurses for the last 20 years who have been active in establishing professional interest groups and patient support and lobbying groups, mean that nurses have had a key influence on health care policy in relation to breast cancer services. Nurses have argued strongly for priority to be given to full disclosure of information about diagnosis, treatment and the long-term consequences of cancer treatment, the need for emotional support and active involvement of women in decisions about their treatment, and issues such as breast recon-

struction, the needs of partners and children, hormone replacement therapy and sexuality and fertility issues to be addressed, as part of treatment and care. There has been an important, albeit largely informal, alliance forged between nurses (who are predominantly women) and women with breast cancer to foster better care.

However, health care and more specifically, cancer services are changing. Contemporary health policy emphasises that women as users of health care should be given a direct voice in determining the shape of services and in making key decisions about their own care. Nurses themselves are being given greater responsibility for delivering care and treatment and may increasingly be leading diagnostic and follow-up services where there will be less direct involvement of doctors. This raises questions about the purpose and desirability of intermediaries between women and their doctors, or the necessity of "advocacy" for women with breast cancer since these may reinforce the status quo rather than promoting different doctor-patient relations and nurses are in any case part of the treatment "establishment". There is also greater questioning of the precise role of specialist nurses and insufficient research available to direct the deployment of specialist nurses. New roles and relationships need to be defined, a focus on evolving the roles of specialist nurses may be fruitful in radically altering the shape of breast cancer services so that they may evolve into the "women centred" services we all desire.

200 INVITED

How recruiting patients to clinical trials affects the doctor/patient relationship

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The effect of recruitment to clinical trials on the doctor-patient relationship is an under-researched area. There is considerable literature examining the quality of informed consent in cancer clinical trials (Joffe M., Lancet 358: 1772-1777, 2001). Most of this however focuses on patient satisfaction with the informed consent process and on patient understanding of the general principles and details that have been supposedly explained to them as part of informed consent (Tattersall M.H., Lancet 358: 1742-1743, 2001). It has been demonstrated that a patient is more likely to agree to participate in a clinical trial if his or her oncologist explains the items included in the informed consent document, and if the oncologist communicates in a reflective, patient-centered, supportive and responsive manner (Albrecht J.L., J Clin Oncol 17: 3324-3332, 1999).

In randomized trial discussions, the physician must begin by explaining the uncertainty surrounding treatment decisions for each patient. It seems clear that this approach alone must affect a patient's understanding of her physician's approach to her situation. The additional time taken surrounding this interaction, by both physicians and nurses, may however provide considerable positive benefit for patients involved in trial recruitment. Some investigators working in this area feel that the accrual process is in fact "embedded within" the longer-term relationship between the physician and the patient, and that the interaction occurring during the consent process is part of an "alliance building" that is built into the ongoing relationship (Ruckdeshel, J.C., J Cancer Edu 11: 73-79, 1996). Certainly, the additional time taken and information given at trial entry, and subsequently through the trial process would seem likely to be generally beneficial for most patients. If the purpose of the trial, the alternatives to trial entry and the risks and benefits of being involved in the trial are clearly explained, then hopefully communication will be enhanced, not only while the patient is participating in the individual trial but during future interaction with her physician, nurse and the rest of her treatment team.

201 INVITED

Influence of the Internet and information on the doctor/patient relationship

Abstract not received.

Thursday, 21 March 2002 16:30–18:00

PROFFERED PAPERS

Adjuvant therapy

202 ORAL

The ATAC ('Arimidex', Tamoxifen, Alone or in Combination) adjuvant breast cancer trial in postmenopausal (PM) women

J.S. Tobias. *UCL Medical School, the ATAC Trialists' Group, London, UK*

Anastrozole (A) is superior to tamoxifen (T) in treatment of postmenopausal (PM) women with early breast cancer (EBC) * first results of the ATAC ("Arimidex", Tamoxifen, Alone or in Combination) trial

Introduction: The ATAC trial evaluated, in a randomized, double-blind design, "Arimidex" (A, 1mg), alone or in combination with T (C), relative to T (20 mg) alone as adjuvant treatment for PM patients (pts) with EBC.

Methods: Pts with operable invasive breast cancer (BC) who had completed primary therapy and were eligible to receive adjuvant hormonal therapy were included. Main endpoints (E) were disease-free survival (DFS) and tolerability. Other E included incidence of contralateral (CL) BC.

Results: 9366 pts were recruited (N=3125, 3116, and 3125 for A, T, and C, respectively). Median duration of therapy was 30.7 mth and median follow-up was 33.3 mth. Total event numbers were 317, 379, and 383 for A, T, and C, respectively. 84% of pts were known to be ER+ and/or PR+. DFS was significantly improved for A vs T (p=0.013). Incidence of CL BC was significantly reduced for A vs T (p=0.007). A was significantly better tolerated than T (endometrial cancer, vaginal bleeding/discharge, ischaemic cerebrovascular events, thromboembolic events, hot flushes and weight gain) ($p<0.03$ for all). T was significantly better tolerated than A (musculoskeletal disorders and fractures) ($p<0.03$ for both).

Endpoint	Comparison	HR*	95.2% CI	p-value
DFS (all pts)	A vs T	0.83	0.71* 0.96	0.013
	C vs T	1.02	0.88* 1.18	0.8
OR** 95% CI p-value				
CL BC (all pts)	A vs T	0.42	0.22* 0.79	0.007
	C vs T	0.84	0.51* 1.40	0.5

* hazard ratio; ** odds ratio

Conclusion: A showed superior efficacy to T for DFS and CL BC. These early findings show A as an effective and well tolerated endocrine option for the treatment of PM pts with EBC. Longer follow-up and long-term data on bone mineral density and cognitive function are required to allow a complete benefit / risk assessment to be made.

203 ORAL

Effect of filgrastim on dose intensity of adjuvant CMF with concomitant radiotherapy in patients with operable breast cancer. A prospective randomized study

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Objectives: We showed previously that patients (pts) receiving concomitant radiotherapy (RT) and adjuvant CMF were at high risk of neutropenic events compromising the achievement of optimal dose delivery. The main goal of this randomized trial is to investigate the ability of filgrastim (r-metHuG-CSF, Neupogen®) to ameliorate total dose delivery and dose-intensity of adjuvant CMF in combination with radiotherapy (RTCT). The effect of filgrastim support on overall and haematological tolerance, haematological parameters at one year after surgery and cutaneous and pulmonary tolerance on RT was also evaluated.

Methods: A cohort of 102 pts with operable invasive breast cancer having completed surgery and initiating adjuvant chemotherapy (CT) with CMF (600/40/600 mg/m* IV, d1&8, q 4w, 6 cycles planned) concomitantly with radiotherapy were registered. At first event affecting dose intensity (ANC $<$ 1500 imposing delay on d1, or reduction on d8 of any cycle), pts were randomized to pursue their CT either with further support with filgrastim.5 μg/kg sc daily, given on days 2 to 6 and 9 to 13 of each remaining cycle (Group A) or without filgrastim, unless for eventual treatment of febrile neutropenia (Group B). The main endpoint was to compare the proportion of