Selected abstracts from: Treating patients with cancer: individualising care

NOVEL THERAPEUTIC APPROACHES FOR *BRCA1* AND *BRCA2* ASSOCIATED CANCERS

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Individuals harbouring germ-line mutations in the *BRCA1* or *BRCA2* genes are at highly elevated risk of a variety of cancers. Ten years of international collaborative research has revealed roles for *BRCA1* and *BRCA2* in a wide variety of cellular processes. However, it seems likely that the function of these proteins in DNA repair, critically important in maintaining genome stability, is crucial to the malignant transformation of cells that have lost function. Despite this increasing knowledge of the defects present in *BRCA*-deficient cells, *BRCA* mutation carriers developing cancer are still treated similarly to sporadic cases.

A mechanism-based investigative approach to therapy will be described that specifically targets the cancer rather than normal tissue genome. This approach is based on understanding the DNA repair defects in *BRCA*-deficient cells, and describes attempts to define both the optimal existing treatment for cancers arising in *BRCA* mutation carriers and the development of novel therapeutic approaches. There are indications that a significant proportion of sporadic breast and ovarian cancers may exhibit deregulation of the *BRCA1* and *BRCA2* pathways. Cancer treatments developed to treat *BRCA*-mutant tumours might be applied to some sporadic cancers sharing similar specific defects in DNA repair, if surrogate markers of '*BRCA*ness' can be identified. Clinical trials addressing these issues will be discussed.

Further reading

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- Reis-Filho JS, Tutt AN. Triple negative tumours: a critical review. *Histopathol* 2008; 52:108–18.
- Edwards SL, Brough R, Lord CJ et al. Resistance to therapy caused by intragenic deletion in BRCA2. *Nature* 2008; 451:1111–5.

Keywords *BRCA1*, *BRCA2*, PARP therapy
Declaration of interests Dr Tutt has received discovery payments relating to PARP inhibitors in *BRCA1*/*BRCA2* cancers in the Institute of Cancer Research's rewards to inventors scheme.

GETTING THE RIGHT PATIENT: BIOMARKERS

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The common route for biomarker discovery is to use fresh/frozen patient tissue. However, archived formalin fixed paraffin-embedded tissue (FFPE) is the standard method of storage of cancer tissue in pathology departments worldwide. If this FFPE tissue could be analysed genetically and then linked to a patient's response to chemotherapy or relapse there would be an accelerated way to create new cancer diagnostics/biomarkers.

During the seminar, Response Genetics' recent gene-profiling studies using FFPE tissue will be discussed for predicting relapse in a number of cancers. Gene studies to predict response to platinum-containing chemotherapy will also be discussed.

Keywords Archived formalin fixed paraffin embedded tissue (FFPE), cancer, diagnostics/biomarkers, gene-profiling
Declaration of interests None declared.

CHEMOTHERAPY-INDUCED CHEST PAIN

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An increasing number of fit patients are now receiving anti-cancer medications, often in the adjuvant context, aiming for ultimate cure. It is increasingly common for at least some of these drugs to be given in oral form and taken at home. It is well recognised that many of these anti-cancer drugs may cause a spectrum of cardio-vascular pathologies, including acute ischaemic chest pain, myocardial infarction, arrhythmias, myocarditis, hypertension, thromboembolic events, cardiac failure or sudden death.[1,2]

The initial management of acute cardiac problems should be in an acute medical admissions setting and should follow chest pain protocols. However, a careful drug history is also essential, and this is under-represented in most acute chest pain protocols.

Fluorouracil (5-FU) or its oral equivalent, capecitabine (Xeloda), is a drug frequently used for the treatment of colorectal, oesophagogastric and breast cancers. It has been shown to cause acute cardiac events in 2–18% of cases.[3] The exact pathophysiology of this is unclear and might result from myocyte damage or coronary artery spasm. Although

more commonly seen in those with underlying cardiac risk factors or known ischaemic heart disease, it is not exclusively so, and coronary angiography can be completely normal despite ECG and cardiac enzyme changes.

Patients who are on 5-FU or oral capecitabine and who present with acute cardiac symptoms must stop these medications immediately. In addition, on resolution of the cardiac event, these drugs should not be restarted until review by the oncology team. There is a high chance of recurrence of symptoms on rechallenge.

References

1 Yeh ETH, Tong AT, Lenihan DJ et al. Cardiovascular complications of cancer therapy. *Circulation* 2004; 109:3122–31.
2 Chu TF, Rupnick MA, Kerkela R et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet* 2007; 15: 370(9604):2011–9.
3 Jensen SA, Sorensen JB. Risk factors and prevention of cardiotoxicity induced by 5-fluorouracil or capecitabine. *Cancer Chemother Pharmacol* 2006; 58:487–93.

Keywords Anti-cancer chemotherapy, acute chest pain, cardiotoxicity, pharmacovigilance
Declaration of interests None declared.

INVESTIGATING AND TREATING PATIENTS WITH UNKNOWN PRIMARY

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Metastatic cancer of unknown primary site (CUP) accounts for approximately 3% of all malignant neoplasms and is therefore one of the ten most frequent cancer diagnoses. Patients with CUP present with metastatic disease for which the site of origin cannot be identified at the time of diagnosis. It is now accepted that CUP represents a heterogeneous group of malignancies that share a unique clinical behaviour and, presumably, unique biology.

Since CUP is not a homogeneous disease and consists of different favourable and unfavourable subsets, treatment of each clinicopathological entity requires a unique approach.

Extensive work-up with specific pathology investigations (immunohistochemistry, electron microscopy, molecular diagnosis) and modern imaging technology – computed tomography, mammography, positron emission tomography scan – have resulted in some improvements in diagnosis; however, the primary site remains unknown in most patients, even on autopsy. The most frequently detected primaries are carcinomas hidden in the lung or pancreas.

Several favourable subsets of CUP have been identified, which are responsive to systemic chemotherapy and/or locoregional treatment. The identification and treatment of these patients is of paramount importance. The considered responsive subsets to platinum-based chemotherapy are the poorly differentiated carcinomas involving the mediastinal-retroperitoneal nodes, the peritoneal papillary serous adenocarcinomatosis in females and the poorly differentiated neuroendocrine carcinomas. Other tumours successfully managed by locoregional treatment with surgery and/or irradiation are the metastatic adenocarcinoma of isolated axillary nodes, metastatic squamous cell carcinoma of cervical nodes or any other single metastatic site. Empirical chemotherapy benefits some of the patients who do not fit into any favourable subset, and should be considered in patients with a good performance status.

Further reading

- Pavlidis N, Briasoulis E, Hainsworth J et al. Diagnostic and therapeutic management of cancer of an unknown primary. *Eur J Cancer* 2003; 39(14):1990–2005.
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- Pavlidis N. Forty years experience of treating cancer of unknown primary. *Acta Oncol* 2007; 46(5):592–601.
- Pentheroudakis G, Golfinopoulos V, Pavlidis N. Switching benchmarks in cancer of unknown primary: from autopsy to microarray. *Eur J Cancer* 2007; 43(14):2026–36.
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Keywords Cancer of unknown primary , chemotherapy
Declaration of interests None declared.

SEPSIS IN CANCER

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Neutropenic sepsis is a common and life-threatening complication of cancer chemotherapy. Broad-spectrum antibiotics have dramatically reduced mortality over the past decades. Future management strategies are aimed at reducing morbidity and hospital stays and increasing the role of risk stratification.

The presentation focuses on neutropenic sepsis in solid tumour patients and describes the presentation and management. Emphasis is placed on the role of risk assessment (MASCC) and the evolving management of low-risk patients, including oral antibiotics, early hospital discharge and the ORANGE trial. The importance of robust patient triage is discussed.

Neutropenic sepsis represents a spectrum of severity, and many patients can be managed safely with low-risk strategies that incorporate initial risk assessment tools. Effective patient triage pathways are essential in reducing mortality and improving patient care.

Keywords MASCC index, neutropenia, oral antibiotics, sepsis, triage
Declaration of interests Dr Marshall is the chief investigator for the CRUK-funded ORANGE trial.