J R Coll Physicians Edinb 2008; 38:251–5

Treating patients with cancer: individualising therapy, improving outcome

CO Michie
Clinical Research Fellow and Specialist Registrar in Medical Oncology, Edinburgh Cancer Research Centre, Edinburgh, UK

ABSTRACT This is an exciting time in the treatment of patients with cancer, as new therapies and technologies begin to impact on patient care. The concept of individualisation of therapy has come to the fore in both clinical practice and in cancer research; this excellent symposium introduced several ways in which new molecular techniques can improve patient selection and aid clinical decision-making. Methodical, evidence-based approaches to common clinical problems in oncology were also presented. It is clear that the challenges now are to investigate and validate which potential new therapeutic targets are important in vivo, and to identify which subgroups of patients benefit most from specific therapies and which patients can be spared treatment and its inherent risk of potential morbidity. In addition to this, by working together to enhance supportive care and reduce toxicity, the ultimate goal of improved outcome for patients can be realised.

KEYWORDS Adjuvant taxane chemotherapy, algorithm for palliation of nausea, archival formalin-fixed paraffin-embedded (FFPE) tumour tissue, biomarkers, *BRCA*-1 and 2 proteins, carboplatin, cardiotoxic effects of 5-fluorouracil and capecitabine, Comprehensive Geriatric Assessment, cytochrome P450, gene expression profiling, irinotecan, metastatic carcinoma of unknown primary site, microarray profiling, neutropenic sepsis, 'p53' neoadjuvant chemotherapy, pharmacogenomics, PARP inhibitor, tamoxifen, UGT 1A1*28

DECLARATION OF INTERESTS No conflict of interests declared.

Published online ***July 2008***

Correspondence to ***CO Michie, Edinburgh Cancer Research Centre, Crewe Road South, Edinburgh EH4 2XR, UK***

tel. ***+44 (0)131 777 3500***
fax. ***+44 (0)131 777 3520***
e-mail ***cmichie@staffmail.ed.ac.uk***

INTRODUCTION

To improve outcomes for people with cancer in the twenty-first century, the concept of individualisation of therapy has come to the fore in both the clinical practice of oncology and in cancer research. Previously, patients were treated as relatively homogenous groups, based on their tumour site of origin. However, it is now clear that each tumour, and each patient, is unique and that a multitude of factors influence tumorigenesis, metastatic potential, treatment tolerance, response and prognosis.

The symposium introduced several strategies for tailoring therapy and discussed ways of approaching the clinical challenge that we now face.

SESSIONS 1 AND 2: PERSONALISING TREATMENTS FOR CANCER

Professor Nicholas Pavlidis (Professor of Medical Oncology, University of Ioannina, Greece) discussed optimal investigation and treatment of patients with metastatic carcinoma of unknown primary site (CUP), the fourth most common cause of cancer-related death.[1] Metastatic CUP represents a heterogenous spectrum of malignancies, but the disease course is characterised by early dissemination, aggressive behaviour, poor prognosis[2] and an unpredictable metastatic pattern.

A clear, evidence-based algorithm was presented to investigate these patients in a timely and cost-effective manner.[3] Despite extensive diagnostic work-up, the ante-mortem frequency of detection of primary site remains at ~30%.[4] In the future, gene expression (microarray) profiling may improve the diagnostic accuracy in identifying tumour origin, but it remains to be seen whether this will improve prognosis for patients.[5]

Treatment decisions must be subsequently made in the absence of a proven primary site. Patients with CUP can be categorised into distinct clinicopathological entities which are divided into favourable (good prognosis) and non-favourable (poor prognosis) subtypes. This distinction can be used to guide treatment decisions and predict prognosis.[3] Response rates in the favourable subsets can approach those seen in other solid malignancies,[4] but unfavourable subsets still respond poorly to currently available drugs. Younger patients with good performance status could be offered platinum-based chemotherapy, but best supportive care or experimental therapies may be acceptable options for many in the poor prognosis group.

Biomarkers

To predict a patient's response to a particular drug or to quantify an individual's risk of recurrence, a well-validated and reproducible biomarker is required. Dr James Clark (Head of European Operations, Response Genetics Ltd)

presented recent gene-profiling studies using techniques to extract genetic information from archival formalin-fixed, paraffin-embedded (FFPE) tumour tissue. While the common route for biomarker discovery has usually been with fresh frozen tumour tissue, paraffin-embedded samples are the standard method of storage in pathology departments worldwide. This increases the applicability of expression array technology and facilitates studies involving large numbers of patients.

How this might impact on clinical care and decision-making was discussed; for example, comparison of tumour gene expression profiles with survival data can identify high-risk genetic signatures. Patients can then be treated accordingly on the basis of their genetic profile, with high-risk patients being recommended further adjuvant therapy and the lower-risk group being spared unnecessary treatment. Response Genetics is currently collaborating with the Edinburgh Cancer Research Centre on evaluating the utility of Excision Repair Cross Complementation Group 1 (ERCC-1) mRNA expression, quantified from FFPE tumour samples, as a predictor of platinum resistance in a large study of patients with epithelial ovarian cancer.[6]

Robust validation of such biomarkers in the setting of large, prospective, randomised clinical trials will be a key step in their development.

Pharmacogenomics

Once a treatment plan has been agreed, administering the correct dose of a drug for an individual patient is fundamental. Professor Howard McLeod (Distinguished Professor of Pharmacy and Medicine, University of North Carolina, and Director, UNC Institute for Pharmacogenomics and Individualized Therapy, Chapel Hill, USA) discussed how pharmacogenetic analysis of patient DNA could aid clinical decision-making by prediction of how a patient is likely to 'handle' a drug. Several genetic polymorphisms are well recognised and can significantly affect treatment outcome.[7–8]

At one end of the spectrum, patients can fail to metabolise drugs such that they are less effective (increased risk of breast cancer relapse in patients with cytochrome P450 2D6 polymorphism receiving tamoxifen[9–10]), while others can have a predisposition to excessive toxicity (increased severity of irinotecan-induced neutropenia and diarrhoea in patients with UGT 1A1*28 polymorphism[11]). Early identification of probable non-responders or those with a high risk of toxicity is recommended, allowing the selection of an alternative treatment strategy, and this would represent a significant advance in the delivery of anti-cancer therapy. Testing for the genetic polymorphisms affecting tamoxifen and irinotecan is increasing in the US as physicians, patients, the FDA and insurance companies recognise the potential impact on quality of life, the likelihood of a successful treatment outcome and healthcare costs.

Identifying patients who benefit

In the field of breast cancer treatment, individualisation of therapy is not a novel one, as hormone receptor status has guided therapy for many years. Professor David Cameron (Director, National Cancer Research Network, University of Leeds) gave an intriguing insight into what the subgroup analyses of the recent EORTC/BIG collaborative 'p53' neoadjuvant chemotherapy trial and the large (>4,000 patients) TACT adjuvant taxane chemotherapy trial tell us. Both reiterate that only a subset of patients benefit from adjuvant treatments,[12–13] highlighting the need to develop prospective strategies to identify these patients and limit unnecessary morbidity and cost.

In addition to clinical outcome, neoadjuvant therapy trials offer an ideal format for the identification of gene signatures representative of chemo-responsive tumours. This was another major objective of the p53 trial, which involved expression microarray analysis of patients' pre- and post-chemotherapy tumour tissue. Data relating to oestrogen receptor negative tumours is already available, and a high negative predictive value was seen.[13] This approach may soon guide clinical decision-making by allowing early selection of non-responders who should be considered for clinical trials of newer agents.

PARP inhibition: a new therapeutic target

Dr Andrew Tutt (Consultant Oncologist and Director, Breakthrough Breast Cancer Research Unit, King's College, Guy's Hospital, London) discussed the exciting development from the laboratory to the clinic of a poly ADP ribose polymerase (PARP) inhibitor, as a novel therapy for patients with *BRCA*-deficient tumours.

DNA repair is one of the major functions of *BRCA*-1 and 2 proteins.[14] Patients carrying a germline mutation retain the ability to repair damage as long as the other remaining normal copy is intact. Tumours frequently develop when this 'wild-type' copy fails in a cell, with resultant error-prone repair and genomic instability. *BRCA*-deficient cells have been shown in the laboratory to be exquisitely sensitive to PARP inhibition,[15] and it is hoped that exploitation of this tumour-restricted DNA defect will translate into improved outcome, both by targeting the tumour cells directly but also sparing the normal tissues. Trials of PARP inhibitors are currently at the phase II stage and have already been shown in a phase I trial to have encouraging anti-tumour activity with minimal toxicity.[16]

While hereditary cancers only represent a minority of breast and ovarian malignancies, research has suggested that a significant proportion of sporadic cases may also involve aberrant *BRCA*-1 and/or 2 pathways, sharing similar defects in DNA repair.[17–18] Therefore, cancer therapies developed to treat *BRCA*-mutant tumours may also be more widely applicable to some sporadic cancers, if appropriate surrogate markers can be

J R Coll Physicians Edinb 2008; 38:251–5

identified. In addition, work is ongoing to evaluate whether patients with *BRCA* deficiency or a *BRCA*-like tumour profile are more likely to respond better to an established DNA-damaging agent such as carboplatin, which is less commonly used in breast cancer, rather than a taxane.[14]

SESSION 3: CHALLENGING CLINICAL SCENARIOS: AGE AND FITNESS

The incidence of cancer rises with advancing age, yet many of the clinical trials that shape daily practice in oncology do not reflect this. Professor Robert Leonard (Clinical Director for Cancer Services, Hammersmith Hospital, London) highlighted the wide spectrum of fitness that can be found in the elderly, and the uncertainties that this can present.

As life expectancy in the UK improves due to the treatment of other illnesses, control of cancer in the elderly will increasingly dictate survival and quality of life. There is a danger of being over-cautious in fit elderly patients. However, it is well recognised that those who are less robust can be at higher risk of toxicity. It is therefore important to assess each patient individually. While gauging performance status remains useful, it can be misleading in a significant proportion of elderly patients. Adoption of the Comprehensive Geriatric Assessment (CGA) tool as a more detailed assessment of an elderly patient's suitability for therapy was encouraged by Prof. Leonard.[19–20] Ultimately, however, treatment decisions can be difficult in this age group as firm evidence is often lacking. Enthusiastic support of clinical trials aimed at elderly patients should help clarify some dilemmas and this should also be promoted.

Conversely, young patients with cancer can present very different challenges. Dr David Dunlop (Consultant Medical Oncologist and Lead Clinician for Chemotherapy Services, Beatson West of Scotland Cancer Centre) discussed how considerable physical, psychological and social factors can impact on the ability to deliver intensive potentially curative treatment safely. Key coping strategies to consider were presented. Negotiation often becomes an essential component of successful treatment in teenagers, as they strive to develop and maintain independence and autonomy. The use of specialist teenage cancer support groups should be promoted in addition to assistance from specialist medical and nursing staff in paediatric oncology.

SESSION 4: THE CANCER PATIENT IN THE ACUTE RECEIVING UNIT AND SUPPORTIVE CARE

The final session covered a number of clinical scenarios that affect cancer patients frequently and often necessitate acute hospital admission. Professor Marie Fallon (St Columba's Hospice Chair of Palliative Medicine, Edinburgh Cancer Research Centre) presented a mechanistic-based management algorithm for palliation of nausea and/or vomiting. A thorough assessment with careful consideration of the likely aetiology, pathway and neurotransmitter(s) involved should lead to selection of an appropriate antiemetic.[21] However, systematic use of different agents which cover a variety of neurotransmitters may be required. A good example of this is in the treatment of chemotherapy-induced emesis, where the recently developed broad spectrum neurokinin-1 (NK1) receptor antagonists have been shown to improve cisplatin-induced delayed emesis when added to dexamethasone and a 5HT3 antagonist.[22–23] In addition, there is evidence for other adjuvant interventions that are also worth considering on an individual basis. Future research is likely to improve our understanding of the various integrated pathways involved and in turn improve our treatment of this often distressing symptom.

Acute confusion occurs in cancer patients for a myriad of reasons. Dr Marianne Nicholson (Consultant Medical Oncologist, Aberdeen Royal Infirmary, and Clinical Lead for Cancer Research, North of Scotland) discussed a logical approach to the investigation and management of this common presenting symptom. In the first instance, a clear history, including the stage of the underlying diagnosis, timing and details of treatment received, and an accurate list of concomitant medications is vital. Assessment should then include routine admission investigations and sign- or symptom-directed specific investigations. Usually treatment should focus on the underlying cause. However, at the end of life the primary goal may be to relieve distress; in this situation good communication with relatives and appropriate palliative care is paramount.

Neutropenic sepsis remains a life-threatening complication of cancer treatment and accounts for many thousands of in-patient bed days per year in the UK. Until recently, much of the research in febrile neutropenia was aimed at reducing mortality or improving response to specific antibiotics. With the success of broad spectrum antibiotics, these are now less relevant. Dr Ernest Marshall (Macmillan Consultant in Clinical Oncology, Clatterbridge Centre for Oncology, Bebington, Cheshire) discussed the organisation of patient triage and presented how his unit has succeeded in reducing costs, nursing time and length of hospital stay by rapidly incorporating the validated and evidence-based Multinational Association of Supportive Care in Cancer (MASCC) Risk Index.[24] Successful treatment should now equate to overall patient benefit, and by reducing the widespread use of unnecessary intravenous antibiotics and prolonged hospital stays, it is likely that toxicity will be reduced and quality of life enhanced. A randomised, phase III, NCRN-supported study, the 'Orange' trial, is currently recruiting patients to further evaluate this hugely important topic.

Several anticancer agents have cardiotoxic effects that can manifest in several ways. Dr Sally Clive (Consultant Medical Oncologist, Edinburgh Cancer Centre) focused on the often neglected but important issue of fluoropyrimidine-induced ischaemia. 5-Fluorouracil (5FU), either as an intravenous preparation or as its pro-drug, capecitabine, is frequently used in the treatment of some of the most common cancers in the UK. It has been shown to cause acute cardiac events in 2–18% of cases,[25] although the pathophysiology remains unclear. Silent ECG changes are also recognised.[26] While more commonly seen in those with underlying cardiac risk factors or established ischaemic heart disease, 5FU-induced ischaemia can also be seen in fit or young patients with subsequently normal coronary angiograms.

These drugs are increasingly being used in an adjuvant context, with the aim of long-term cure. Cardiotoxicity can therefore have significant clinical implications for cancer control as it is vital that major cardiac events are minimised and, unfortunately, the re-treatment risk of further toxicity is 82–100%. A postal questionnaire of UK oncologists found that there is considerable variation in the management of these patients, with no agreed policy in most centres.[27] What is clear is that patients receiving these agents who develop acute cardiac symptoms must stop the drug immediately. However, as chemotherapy-induced ischaemia is an uncommon cause of all patients presenting to acute units with chest pain, increasing awareness and early communication across specialties are essential.

CONCLUSION

This is an exciting time in the treatment of patients with cancer, as new therapies and technologies begin to impact on patient care.

A recurring theme of this symposium was the discussion of how new molecular techniques can improve patient selection and aid clinical decision-making. It is clear that the challenges now are to investigate and validate which potential therapeutic targets are important in vivo, to identify which subgroups of patients benefit most from specific therapies and which patients can be spared treatment and its inherent risk of potential morbidity. In addition to this, by working together to enhance supportive care and reduce toxicity, the ultimate goal of improved outcome for patients can be realised.

Acknowledgements

The symposium was organised by Professor Duncan Jodrell, Dr Charlie Gourley, Dr Larry Hayward, Dr Lucy Wall and Dr Leslie Samuel with help and encouragement from Professor John Smyth. Thank you also to Professor Jodrell for critical review of this manuscript.

EDUCATION

REFERENCES

1 Pavlidis N, Fizazi K. Cancer of unknown primary (CUP). *Crit Rev Oncol Haematol* 2005; 54(5):243–50.
2 Bishop JF, Tracey E, Glass P et al. Prognosis of sub-types of cancer of unknown primary (CUP) compared to metastatic cancer. *J Clin Oncol* 2007; 25(18S):21010.
3 Briasoulis E, Pavlidis N. Cancers of unknown primary site: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Annals Oncol* 2007; 18(S2):ii81–2. Available from: http://www.esmo.org/resources/clinicalguidelines/
4 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.
5 Pentheroudakis G, Golfinopoulos V, Pavlidis N. Switching benchmarks in cancer of unknown primary: from autopsy to microarray. *Eur J Cancer* 2007; 34(14):2026–36.
6 Michie CO, Clark JS, Hoffman AC et al. ERCC-1 gene expression as a predictor of outcome following platinum-based chemotherapy in epithelial ovarian cancer (EOC). *J Clin Oncol* 2008; 26 (May 20 suppl): abstr 5564.
7 Evans WE, McLeod HL. Pharmacogenomics – drug disposition, drug targets and side effects. *N Engl J Med* 2003; 348:538–49.
8 Weinshilboum R. Inheritance and drug response. *N Engl J Med* 2003; 348:529–37.
9 Goetz MP, Rae JM, Suman VJ et al. Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. *J Clin Oncol* 2005; 36:9312–8.
10 Goetz MP, Knox SK, Suman VJ et al. The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. *Breast Cancer Res Treat* 2007; 101(1):113–21.
11 Hoskins JM, Goldberg RM, Qu P et al. UGT1A1*28 genotype and irinotecan-induced neutropenia: dose matters. *J Natl Cancer Inst* 2007; 99:1290–5.
12 Ellis PA, Barrett-Lee PJ, Bloomfield D et al. Preliminary results of the UK Taxotere as Adjuvant Chemotherapy (TACT) trial. 30th Annual San Antonio Breast Cancer Symposium 2007: abstract 78. Available from: http://www.abstracts2view.com/sabcs/
13 Bonnefoi H, Potti A, Delorenzi M et al. Validation of gene signatures that predict the response of breast cancer to neoadjuvant chemotherapy: a substudy of the EORTC 10994/BIG 00-01 clinical trial. *Lancet Oncol* 2007; 8:1071–8.
14 Kennedy RD, Quinn JD, Mullan PB et al. The role of BRCA1 in the cellular response to chemotherapy. *J Natl Cancer Inst* 2004; 96(22):1659–68.
15 Farmer H, McCabe N, Lord CJ et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature* 2005; 434(7035):917–21.
16 Yap TA, Boss DS, Fong PC et al. First in human phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of KU-0059436 (Ku), a small molecule inhibitor of poly ADP-ribose polymerase (PARP) in cancer patients (p), including BRCA1/2 mutation carriers. *J Clin Oncol* 2007; 25(18S):3529
17 Turner NC, Reis-Filho JS. Basal-like breast cancer and the BRCA1 phenotype. *Oncogene* 2006; 25:5846–53.
18 Turner NC, Reis-Filho JS, Russell AM et al. BRCA 1 dysfunction in sporadic basal-like breast cancer. *Oncogene* 2007; 26:2126–32.
19 Extermann M, Aapro M, Bernabei R et al. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of

Geriatric Oncology (SIOG). *Crit Rev Oncol Haematol* 2005; 55(3):241–52.
20 Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. *J Clin Oncol* 2007; 25(14):1824–31.
21 Lichter I. Which antiemetic? *J Palliat Care* 1993; 9(10):42–50.
22 Hesketh PJ, Grunberg SM, Gralla RJ et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin – the Aprepitant Protocol 052 Study Group. *J Clin Oncol* 2003; 21(22):4112–9.
23 Hesketh PJ, Van Belle S, Aapro M et al. Differential involvement of neurotransmitters through the time course of cisplatin-induced emesis as revealed by therapy with specific receptor antagonists. *Eur J Cancer* 2003; 39(8):1074–80.
24 Klatersky J, Paesmans M, Rubenstein EB et al. The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol* 2000;18(16):3038–51.
25 Jensen SA, Sorensen JB. Risk factors and prevention of cardiotoxicity induced by 5-fluorouracil or capecitabine. *Cancer Chemother Pharmacol* 2006; 58:487–93.
26 Rezkalla S, Kloner RA, Ensley J et al. Continuous ambulatory ECG monitoring during fluorouracil therapy: a prospective study. *J Clin Oncol* 1989; 7:509–14.
27 McGoldrick T, Clive S, Jodrell DI. National survey of fluoropyrimidine induced cardiac ischaemia. *National Cancer Research Institute UK Annual Conference Proceedings* 2007: abstr B109. Available from: http://www.ncri.org.uk/ncriconference/abstract/pdf/2007%20pdfs/B109.pdf