Editors' view

Cancer therapeutics revisited; novel drugs targeting cell signalling pathways, genome wide association studies and other trials and tribulations

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In 2006 the *Journal* published a themed issue on cancer therapeutics [1]. Recognizing both the number and speed of advances in the scientific understanding of the molecular basis of cancer, we felt it timely to revisit and focus on anti-cancer therapy in a themed section of the *Journal*. Hanahan & Weinberg [2] have provided an elegant summary of our modern understanding of the complex cellular biology which differentiates cancer cells from normal cells. These differentiating characteristics provide druggable therapeutic targets including several kinase enzymes. Targeted tyrosine kinase inhibitors (TKIs) are effective in treating certain cancers and have been adopted into standard-of-care treatments (e.g. imatinib in chronic lymphocytic leukaemia, sunitinib in renal cell carcinoma). The clinical development of agents targeting some of the more recently defined cell signalling pathways, has the potential to expand further our anti-cancer therapeutic armamentarium.

From cell cycle checkpoint (Chk) inhibitors and pro-apoptotic drugs to the role of genome wide association studies (GWAS)

Thompson & Eastman [3] remind us that many classical anticancer agents damage DNA and this activates cell cycle checkpoints, allowing time for the cells to repair their DNA and recover. The proteins involved in these checkpoints have undergone intense investigation as potential therapeutic targets and Chk1 inhibitors have emerged as promising novel therapeutic agents. Chk1 was initially recognized as a regulator of the G2/M checkpoint, but has

since been demonstrated to have additional roles in DNA replication fork stability, replication origin firing and homologous recombination. Inhibition of these checkpoints can dramatically sensitize cells to some antimetabolites. Several current clinical trials with Chk1 inhibitors involve combination with gemcitabine. In pre-clinical models and in humans, gemcitabine causes tumour cells to accumulate in S phase for at least 24 h before recovering. The authors suggest that to optimize the dose and schedule of Chk1 inhibitors and antimetabolite combinations there is a need to assess cell cycle perturbation and Chk1 dependence of tumours in patients.

Apoptosis is derived from the Greek and means 'dropping off' or 'falling off' in reference to petals or leaves. In modern scientific terms it refers to the process of 'programmed cell death'. Bates & Lewis [4] guide us in a comprehensive manner through the cellular apoptosis signalling pathway. They focus on discussing the development of drugs targeting proteins in this pathway that tip the balance of signalling towards cell death. Preclinical and preliminary clinical evidence is presented that drugs that inhibit the anti-apoptotic *Bcl-2* family proteins or are antagonists of the inhibitors of apoptosis proteins (IAPs) offer significant potential for the treatment of patients with lymphoma and/or leukaemia.

Patel *et al.* [5] discuss the implications and current status of GWAS in cancer therapy, in particular germ-line mutations. They draw our attention to genetic loci which appear to predict cancer drug toxicity or treatment outcome. Notable examples include SNPs in the *FGD4* gene that were associated with the development of paclitaxel-related neuropathy in breast cancer patients, and the SNP in the *IL17F* gene that was associated with a

reduction in median overall survival of 3.7 months in patients with pancreatic cancer treated with gemcitabine, with or without bevacizumab. Appropriately the authors highlight the lessons learnt and future challenges in cancer GWAS, specifically the need for functional analysis of genetic variants, prospective replication of findings in clinical trials, as well as future perspectives for biological significance and clinical application of the findings.

Cancer drug pharmacokinetic interactions and population PK–PD

Herbal medicines or nutraceuticals are often widely used by cancer patients, with little information available as to the potential of these products to interact with and modulate the efficacy/toxicity of concurrently administered anti-cancer drugs. Perhaps the best example of this was St John's Wort inducing the metabolism of SN-38, the active metabolite of irinotecan and reducing patients' exposure to the active cytotoxic entity [6, 7]. Goey *et al.* [8] extend *in vitro* observations that *Echinacea purpurea* induces hepatic CYP3A enzyme activity (probably by activation of the pregnane X-receptor) and address the hypothesis that *Echinacea* associated CYP3A enzyme induction reduces exposure of the prototypical CYP3A anti-cancer drug substrate, docetaxel, and consequently potentially reduce its efficacy. A European *Echinacea* product (EchinaForce®) was studied in a non-placebo controlled, sequential crossover study in 10 cancer patients treated with docetaxel monotherapy. The authors observed no significant effect of *Echinacea* on intravenous docetaxel exposure (AUC), elimination half-life or maximum concentration. Some degree of caution should be used in interpreting these findings, since the precise chemical content of this *Echinacea* product was not independently confirmed. In addition the effect of this *Echinacea* product will need to be studied on other oral anticancer molecularly targeted drugs (e.g. TKIs that also are CYP3A substrates) before concluding that they could be safely co-administered with *Echinacea purpurea*. Furthermore it is possible that other *Echinacea* products might contain chemical entities (e.g. hypericin) that are known to induce CYP3A activity.

Coon van Hasselt *et al.* [9] inform us more about the population PK–PD of eribulin mesilate, a non-taxane microtubulin inhibitor, which is approved for the treatment of late stage metastatic breast cancer. Neutropenia is one of its dose limiting toxicities. By combining pharmacokinetic and pharmacodynamic data from 12 phase I, II and III studies of eribulin, the authors defined a semi-physiological PK–PD model for eribulin associated neutropenia. They also determined that the only clinically predictive covariate of inter-individual variability in eribulin PK–PD was serum albumin and generated eribulin dosing guidelines to optimize dose for neutropenia, based on expected changes in model parameters. These guidelines could be clinically

useful, but will need prospective validation, before they can be widely adopted into clinical practice.

In a letter to the Editor, Azzopardi *et al.* [10] present data on the effect of plasma exchange on rituximab (anti-CD20 monoclonal antibody) pharmacokinetics in two patients with lymphoma. Not unexpectedly, based on sparse rituximab plasma concentration data and simulation modelling, plasma exchange reduced rituximab AUC by 38% in patient 1 on day 54 and by 10% in patient 2 on day 274. The authors appropriately recommend that if rituximab treated patients undergo plasma exchange, it should be performed as close to the end of the dosing interval as possible.

Do bisphosphonates reduce the relative risk of colon cancer?

Two independent groups of researchers, suggest that treatment with bisphosphonates is associated with a reduction in the risk of colon cancer. Ma *et al.* [11] undertook a meta-analysis of four case control studies and two cohort studies published between 2010 and 2012. They report a relative risk of colon cancer in patients with any use of bisphosphonates of 0.80 (95% CI 0.75, 0.84), but they did not define a trend to greater risk reduction with duration of use. Bonovas *et al.* [12] undertook a meta-analysis of eight large population-based epidemiological studies (one case-control, two nested case-control analyses within a cohort and five cohort studies). The analysis revealed a significant protective association between bisphosphonate use and colorectal cancer risk (fixed RR = 0.85, 95% CI 0.80, 0.90; random RR = 0.85, 95% CI 0.75, 0.96). These researchers found evidence of a bisphosphonate exposure/dose effect. Clearly a more definitive answer to this issue will only be provided by a rigorous prospective double-blind randomized controlled study of bisphosphonate treatment in patients who are at high risk of colon cancer (e.g. those with multiple benign colonic polyps).

Meta-analyses of adverse cardiovascular effects of modern anti-cancer drug therapy

The cytotoxic antimetabolite, gemcitabine, has been reported to be associated with serious cardiovascular thromboembolic events [13]. The FDA product labelling states that thromboembolic events were reported in 2% of gemcitabine treated patients. Qi *et al.* [14] report a meta-analysis of published phase 2 and phase 3 studies ($n = 19$, 4845 patients) of gemcitabine vs. non gemcitabine containing regimes. The associated odds ratios for venous and arterial thromboemboli were 1.56 (95% CI 0.86, 2.83, $P = 0.15$) and 1.82 (95% CI 0.89, 3.75, $P = 0.10$), respectively, compared with non-gemcitabine-based therapy. The authors concluded that in patients with solid tumours who

receive gemcitabine, there is no significant increase in the risk of venous or arterial thromboemboli when compared with non-gemcitabine based chemotherapy. However, the confidence intervals do not exclude an effect of the magnitude suggested in the product labelling and thus 'more work is needed'.

Several multi-targeted vascular endothelium growth factor receptor tyrosine kinase inhibitors (VEGF-TKIs, e.g. sunitinib, pazopanib, vandetanib, axitinib) are now used clinically to improve survival in patients with vascular tumours such as renal cell carcinoma. A common clinical problem that is encountered in treating patients with these agents is the development or exacerbation of hypertension. Qi *et al.* [15] report on 10 trials (1093 patients) involving treatment with axitinib. The use of axitinib was associated with a significantly increased risk of all grade (RR 3.00, 95% CI 1.29, 6.97, $P=0.011$) and high grade hypertension (RR 1.71, 95% CI 1.21, 2.43, $P=0.003$). The risk of all grade hypertension with axitinib was similar to that with pazopanib (RR 1.05, 95% CI 0.95, 1.17, $P=0.34$), but higher than other commonly used TKIs.

In both these papers, as with all meta-analyses, a degree of caution should be used in interpreting the final results, as there are always potential biases because of the criteria used to select the studies included in the fixed effect or random effect modelling and the missing or incomplete outcome data.

Regulatory approval processes for oral molecularly targeted anti-cancer agents

One of the many unanticipated effects of the modern information technology revolution has been to increase pressure on regulatory agencies to make effective novel anti-cancer agents rapidly available to prescribers and thus cancer patients. Shah *et al.* [16] present a comparison of the regulatory processes of the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) relating to receptor targeted TKIs. The FDA granted priority review to 12 TKIs but the EMA did not grant the equivalent accelerated assessment to any. The FDA granted accelerated approvals to six (38%) and the EMA granted (the equivalent) conditional approvals to four (29%) drugs. Active review times were similar (205.3 days in the US and 225.4 days in the EU). Post-marketing data, however, have suggested reduced efficacy and concerning safety data in the case of gefitinib and lapatinib, indicating the potential downside of expedited approvals. The authors challenge the widely held viewpoint that early regulatory approval and hence early access translates into a beneficial impact on patient health.

This themed issue of the *Journal* clearly demonstrates the full spectrum of how clinical pharmacology continues to contribute to a better understanding of anti-cancer therapy for our patients in the early 21st century.

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