Editorial

‘Old Kerr’s Almanac’

Introduction

So, Farewell, then, Franco Cavalli, clinician, scientist, politician and journalist – except, not quite. Thankfully Franco will continue to write the News Section, that much-liked and much-read part of *Annals of Oncology* which allows Franco to exercise his literary skill. The dominant role of any editor is to superintend publication of the articles which comprise their journal, and ensure truth, quality and relevance. Clearly, *Annals of Oncology* has a series of well defined scientific objectives all of which stem from its central role to report and promulgate high quality clinical and translational oncologic science. One would imagine that this relatively narrow intellectual base would prevent the editorial staff from crusading against social injustice, or campaigning to right wrongs, however Franco has always managed to weave these themes through the News Section. He has provided a strong platform for the new editorial team to develop *Annals of Oncology* and attract research of ever increasing quality, the truest reflection of the Journal’s worth.

So, what of the future? We have a new editorial team, a streamlined process which will increase the speed with which papers can be published and will encourage colleagues to continue to support the journal by sending us their research. Instead of dwelling solely on the future of the journal, I thought that it would be interesting to speculate a little on how oncology might change over the coming decade. I sense you already thinking that ESMO has appointed a despot who will use the editorial fronts piece to rant, rave and thunder at the world and abandon academic logic and neutrality to pursue some personal agenda. Although there is a power when faced with an empty page which, when filled, will be read by others (we hope!), and an associated rush of blood to the nether regions, the overwhelming sense is of duty mixed with intellectual curiosity. So at risk of appearing like a narrowed Nostradamus, I thought it worthwhile making a few guesses as to which themes might emerge over the next decade which could alter our practice of oncology throughout Europe.

Delivery of cancer services

There is some evidence and considerable pressure to suggest that we need to develop more seamless pathways of cancer care. In the past, most clinical services are supplied vertically, in a rather compartmentalised way, with relatively little integration and with many ‘hand-offs’ or transfer of patients from one team to the next e.g., surgeon → radiotherapy → medical oncology → follow-up etc. Most health care systems which operate in Europe fail to recognise that the patient travels horizontally. If we are to develop a Europe without frontiers and passports we must pay greater attention to integrated cancer care pathways. The key factors which will allow us to deliver optimal cancer care include the following:

1. Tumour site specialisation, by surgeons certainly, and increasingly by non-surgical oncologists.
2. Multidisciplinary team working in which there are regular meetings of all the healthcare professionals involved in patient care (surgeons, oncologists, radiologists, pathologists, specialist nurses etc) so that treatment plans can be agreed, mapped out and the patient informed.
3. Site specific, nationally agreed clinical guidelines which are evidence based, peer reviewed and provide current best treatment options for different stages of disease allow a more homogeneous approach to cancer therapy. Of course, guidelines can also act as a framework for nationally important trials and should be dynamic and responsive to the availability of new evidence.
4. IT networks, CD ROM or web based, to provide prospective data collection and cancer registration, can also be used to construct a means of delivering referral guidance between primary and secondary healthcare, or as a means of presenting treatment guidelines in an interactive and dynamic way.

These sorts of changes in delivery of care should contribute to reducing some of the recognised inequities in cancer survival when comparing different European countries.

Clinical trials

The design of phase I trials is periodically modified and we have seen pharmacokinetically guided dose escalation schemes, intrapatient dose escalation and attempts to use Bayesian forecasting methods to make prior assumptions about the maximum tolerated dose, however, the most exciting innovations in phase I trialology will come from inclusion of pharmacodynamic or mechanistic endpoints. If knowledge is power, the more we understand of any novel agent’s mechanism of action, the better we will be able to titrate drug dose against a rational endpoint.

There will be an enormous amount of phase II-type trial activity investigating every possible permutation of the ‘new’ agents which have been licensed over the past
five years and this will continue to engage the clinical community, easily for the next five years. Why? Partly because there are several novel active agents and statistically there probably are hundreds of different combinations which could be developed and tested in different disease sites, however the dominant factor is the complete lack of co-ordination on an international basis for this work and it may be that a trials register, again web site based and open to all, would prevent needless duplication. I also find myself increasingly attracted to randomised phase II studies and I would guess that these will become increasingly common, and again, one could imagine that it may be a way of inducing greater collaboration in the phase II arena.

Although there is an increasing tendency for the academic trials community to be faced with an ever-enlarging bureaucracy over the conduct of clinical trials, it is likely that there we will find a middle route between the extremes of a pharmaceutical company sponsored registration trial and ultra-simple pragmatic trials, which ensure data quality and maximise trial recruitment. Again, it is likely that we will see more pragmatic approaches taken to trial design and see increasing intergroup collaboratives, pioneered in Europe by Jacques Wils and the PETACC trialists, with a view to reducing trial recruitment times and enhancing trial capacity and turnover so that many more innovative questions might be addressed.

**Translational research**

There continues to be a shift towards mechanistically novel anticancer agents away from more traditional inhibitors of DNA synthesis. This has resulted from exploitation of high throughput screens using sophisticated, robotic assays for specific enzymes or molecular binding interactions, in order to select novel chemicals from existing or newly synthesised chemical libraries. These methodologies will be equally applicable to developing screens for DNA binding agents which will activate or repress promoter motifs to allow switching on-off of specific structural genes.

By far and away the largest, looming event which will forever alter the future of medical practice is completion of the human genome project. Having overcome the sequencing barrier there are two subsequent major issues, one scientific the other clinical. There needs to be major downstream investment in structural chemistry, bioinformatics, cellular physiology and protein biochemistry to fully exploit the human genome project from the basic science viewpoint. Clinically, there will be prognostic and therapeutic spin offs. Already, with chip technology, it is possible to prepare arrays of DNA sequences (several thousand on a single chip) which can be inserted into assays which give us a snapshot of which genes are up/down regulated in any given tumour. Prospective studies of these huge data sets mean that without knowing the function of the genes involved, we will be able to use pattern recognition software to relate multiple gene transcription profiles to outcome, chemosensitivity, etc. This methodology could be developed to the point where it becomes standard technology for any pathology laboratory.

The dominant therapeutic challenge is to develop DNA as an anticancer agent. Advances in viral and non-viral delivery of DNA means that gene therapy is likely to advance beyond the current range of phase I or proof of principle studies. Gene replacement studies (e.g., wild-type p53), immune manipulation (e.g., transfection of autologous tumour cells with co-immunostimulatory molecules like B7.1) and gene directed enzyme prodrug therapy (delivering the gene encoding a non-mammalian enzyme which can catalyse conversion of an inactive prodrug to a cytotoxic species) are likely to form the major clinical trial pathways.

Fantastic insights into the molecular and cellular basis of antigen presentation and responsiveness have led to an enormous increase in the range and number of trials of novel, rational immunotherapies. Peptide, genetically engineered vaccinia virus and activated dendritic cell vaccination strategies are being employed alongside adoptive transfer of antigen specific cytotoxic T lymphocytes in a range of solid tumour types, although it is likely that melanoma will remain the most common testbed for immunotherapy.

The future's bright, let's capture it with *Annals of Oncology*.

D. Kerr, MD, DSc, FRCP
Birmingham, UK