

Keynote Lecture:

The Contemporary Impact of Cancer Research on the Diagnosis and Treatment of Cancer

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Introduction

The success of research into the causes and treatment of cancer over the past two decades have recently resulted in genuine changes to practice, with enhanced ability to treat resulting in improved outcomes for patients. The reality of this however is that the workload for health care professionals, doctors, nurses etc, will increase considerably given the growing range of treatments and follow-up necessary to cope with the delivery of modern cancer care. The consequences of this are that we have reached a stage when not everything that is potentially available can be provided and choices sometimes very difficult choices have to be made. The research referred to encompasses prevention, screening, diagnosis and treatment.

Prevention

It is now clearly established that lifestyle factors can influence the development of cancer. The most obvious example of this is the use of cigarette smoke and it is gratifying that public health campaigns are now at long last influencing cigarette smoking in many parts of the world. As an adopted Scotsman I am particularly proud of the fact that smoking in public places is soon to be totally banned in Scotland! Diet, alcohol consumption and inappropriate exposure to sun are further examples of evidence base for the potential prevention of cancer. The concept of developing vaccines against cancer is not new but recent phase III clinical trials have shown that there is now a genuine possibility of preventing carcinoma of the cervix and immunisation programmes are to begin in the very near future. This is exciting progress from research but unfortunately will considerably increase workload since the population to be vaccinated are pre-teenage girls and clearly there are cohorts of teenagers and young women whose cervical smear monitoring will have to continue for 10-20 years. The evaluation of vaccine therapy will also require long-term follow-up.

Screening

Several talks at this symposium have addressed the genetic identification of people at high risk of developing cancer. This field of research is beginning to influence diagnosis and management but is very much work in progress. Importantly the detection of pre-clinical cancer increases workload by providing cohorts of the population who need long-term follow-up to assure that the detection of early disease has truly prevented its clinical manifestation. Where such early detection leads to chemoprevention there will be a change in emphasis of the safety issues associated with chronic drug administration, and again the necessity for long-term follow-up which increases workload will result in the need for choices as to what can and cannot be afforded.

Diagnosis

Research in many fields of biomedicine is now having an impact on the diagnosis of cancer. A particular example in pathology is the development of immunohistochemistry which can greatly refine the diagnosis of for example, adenocarcinomas presenting without

an obvious primary site, or distinguish between cancers in the ovary that might be primary or metastatic from the colon. Developments in imaging particularly with magnetic resonance, PET and greater use of ultrasound significantly enhance our ability to detect cancer, to stage patients and define for example, operable versus inoperable tumours. The use of sentinel node imaging in breast cancer discussed at this meeting is a good example of this, as are the refinements of brain scanning for the selection of operable metastatic cancers in the brain.

Treatment

The conventional role of determining a histopathological diagnosis of cancer and staging the patient for both prognosis and treatment is now being complimented by genetic analysis of tumour biopsies. The detection of specific mutations is beginning to inform prognosis and therefore possibly treatment strategies, and there is a vast industry of expression profiling where work in progress is attempting to categorise patients for both prognostic and treatment selection strategies.

Conventional therapies of surgery, radiation and chemotherapy have for a long time been complimented by hormones and cytokines, but we are now adding signal transduction inhibitors and anti angiogenic strategies in clinical practice as well as in ongoing research. Improvements in surgical treatment are focused on preserving organs that were previously sacrificed for example, limb sparing treatments for osteogenic sarcoma, and particularly conservative operations for breast cancer in comparison to the previous era of mastectomy. The management of breast cancer has been revolutionised by research into neoadjuvant treatment and surgical technical developments to reconstruct the breast with infinitely better cosmetic results than those achieved by more radical surgery in the past. The consequence however of this improved quality of care is that the time taken for such surgical interventions and the manpower involved is considerably increased and therefore there is additional cost.

Where chemotherapy is concerned there have been considerable changes to practice in recent years resulting from the very considerable investment in both academic and industrial research to develop less toxic and more effective medicines. The example of Herceptin for the management of HER2-positive breast cancer is highly topical. 15-20% of women with breast cancer have HER2 positive disease, and the recent publication of results of the HERA trial have excited the profession and patients alike with positive results for treatment with Herceptin in the adjuvant setting. In the United Kingdom there is much political debate about the early public release of trial data resulting in women demanding treatment with Herceptin before it has been to the appropriate licensing authorities, or Health Technology Assessment (NICE) to decide its priority in comparison to other challenges for health care expenditure.

The study of oncogenes is now resulting in changes in clinical practice where the classical example is of the development of Gleevec for the treatment of chronic myeloid leukaemia. Identification of the biochemical consequences of the translocation activating the Bcr-Abl gene resulted in the target whose inhibition proved dramatically successful in controlling chronic myeloid leukaemia.

The pharmaceutical industry has invested very considerable sums of money in the study of signal transduction where the challenge is to identify a key pathway whose

pharmacological interruption can be shown to have therapeutic benefit. In our studies in Edinburgh we have identified RAF1 expression as correlating independently with prognosis in women with ovarian cancer using immunohistochemistry on tumours resected from newly diagnosed patients. Those with a high level of RAF1 expression survived less well in comparison to equally staged and treated women whose RAF1 expression was less significant. A number of RAF1 inhibitors are in development and these will prove interesting as potential new approaches to the management of ovarian cancer. Less close to changes in clinical practice research into the function of tumour suppressor genes is pursued as a new strategy for more selective therapies. Colleagues in Edinburgh have shown that chromosome 11 a site of loss of heterozygosity in patients with epithelial ovarian cancer, where we identified 11q25 as the site of the OPCML gene which is frequently somatically inactivated and has all the functional characteristics of a tumour suppressor gene. Using the nude mouse model carrying the human ovarian cancer line SKOV-3, we find that the parent line lacking OPCML grows successfully in this model but the transfection of functional OPCAM results in significant growth retardation. Functional studies in progress suggest that this gene is responsible for the invasiveness of human ovarian cancer and strategies to reintroduce functional OPCAM are being researched.

The examples mentioned in this paper and in other papers in this excellent symposium show that we can now research the metabolic pathology of human tumours, identifying for example the activation of oncogenes and the loss of tumour suppressor genes. This has already produced clinically proven selective inhibitors of activated oncogenes. In the laboratory research continues to explore the possible restoration of function of lost tumour suppressors. All of this gives genuine optimism for the introduction of new more selective, less toxic therapies which are likely to compliment rather than replace existing conventional therapies of surgery, radiotherapy and chemotherapy. The advantage will be to refine prognosis and produce much more customised treatment combinations for the benefit of an ever increasing number of patients.

Where are we now?

The results of cancer research have clearly improved our ability to prevent cancer for example, with vaccines of cancer of the cervix and to improve screening and early diagnosis for example, with progress in imaging. We are already seeing the concept of more individualised treatment for example, Herceptin in breast cancer. The positive outcome for this is that we should be able to make better use of expensive resources and avoid producing unwanted side effects for patients who cannot respond to treatment. The problem however is that no society in the western world can afford all of this potential treatment and therefore we have to address the very real challenge of setting priorities. But who should set such priorities – clearly this should not be left to the medical profession alone, certainly not politicians alone and despite the importance of listening to patients and their advocates, the very vulnerability of patient's councils against over dependence on different patient lobbying groups. The public at large must take part in this essential debate not least because we are all at risk of developing cancer and almost every family is touched by cancer in one way or another. I strongly encourage the creation of a Health Forum to examine the complexity of setting priorities in health care I believe that this can only be addressed on a national basis given the differences in availability of manpower and technical facilities in different countries and the different health care priorities already established in different member states throughout Europe. Progress in medical research is inevitable – we would be well advised to address this challenge sooner rather than later.