

Cancer Chemotherapy

Rachel Airley

Cancer Research Scientist and Lecturer in Pharmacology

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Preface

While researching this book, I came across a letter in the journal *Nature* asking for caution in the current trend for the use of humorous nomenclature for newly discovered genes¹, the author referring to the tumour suppressor gene *Pokemon*, which I have briefly described in Chapter 4. In this letter, the author reminded us that at a certain point, this name might have to be used by a health professional when discussing a clinical condition with a patient, a sobering thought that served as a reminder that every process started in the laboratory, however prolonged and seemingly removed from the clinic, potentially impacts on the lives of patients. I decided to compile this book after being asked on a number of occasions by pharmacy students at the School of Pharmacy and Chemistry, Liverpool John Moores University if there were a book available that offered a concise, relatively inexpensive and broad introductory text that covered the content of my lecture course in cancer chemotherapy. Specifically, their requests usually came following lectures describing the design, pharmacology and clinical development of novel anticancer agents for which there appeared to be only a limited range of reference sources suitable for undergraduates that didn't involve lengthy searches through the scientific journals. The research and treatment of cancer is a three-way collaboration between health professionals, clinical and experimental scientists, so I have tried to offer a text that unites the topics most pertinent to each group in order to foster a mutual understanding of the role of each at undergraduate level. To this end, the book is aimed at undergraduates of pharmacy, medicine, dentistry, nursing and the allied health professions; as well as providing a useful primer for those considering a career in cancer research, whether they are undertaking a final year dissertation or graduate research project in this area. I have attempted to summarize and consolidate the process behind the research and treatment of cancer, covering topics that range from the clinical aspects of cancer, such as its epidemiology and the role of the many of health professionals involved in its treatment, through to the currently accepted cancer chemotherapy regimens, in particular the classical cytotoxic anticancer agents

¹Maclean, K. (2006) Humour of gene names lost in translation to patients. *Nature*, **439** (7074), 266.

and how they are applied according to cancer diagnosis and staging. I have devoted a large part of the book to the science of cancer research, encompassing basic research into the molecular pathways determining the course of the disease and the methodologies used in target validation, drug discovery and clinical trials. I have also included sections that represent the current state of the art of novel anticancer drug discovery and development. This covers what I would describe as targeted agents, such as the tyrosine kinase inhibitors, some of which have generated excitement and controversy in mainstream newsrooms in recent times. Cancer research is a rapidly evolving field, and although I have made every attempt to provide the most up to date information, it is inevitable that by the time this book comes to publication there will have been further important developments. In order to keep up to date with the progress of novel anticancer agents, I would recommend the web site www.clinicaltrial.gov, and to keep track of newly approved novel agents, the Food and Drug Administration web site provides a search facility www.fda.gov/search/databases.html. Finally, I have included some worked examples of structured essay questions, where I have tried to offer advice that goes beyond the regurgitation of complex chemical structures and offer some insight into exam technique.

It just remains for me to acknowledge the support I have had during this project; at Wylie, my commissioning editor Rachael Ballard and project editor Fiona Woods, who have both showed endless patience through many delays associated with transatlantic moves and working as a real life pharmacist; and the constant support through each new academic challenge of my parents Lorraine and Alan Airley MRPharmS. I would also like to thank the students at Liverpool John Moores University, now also real life pharmacists, who provided me with the original idea for this book.

R.A.

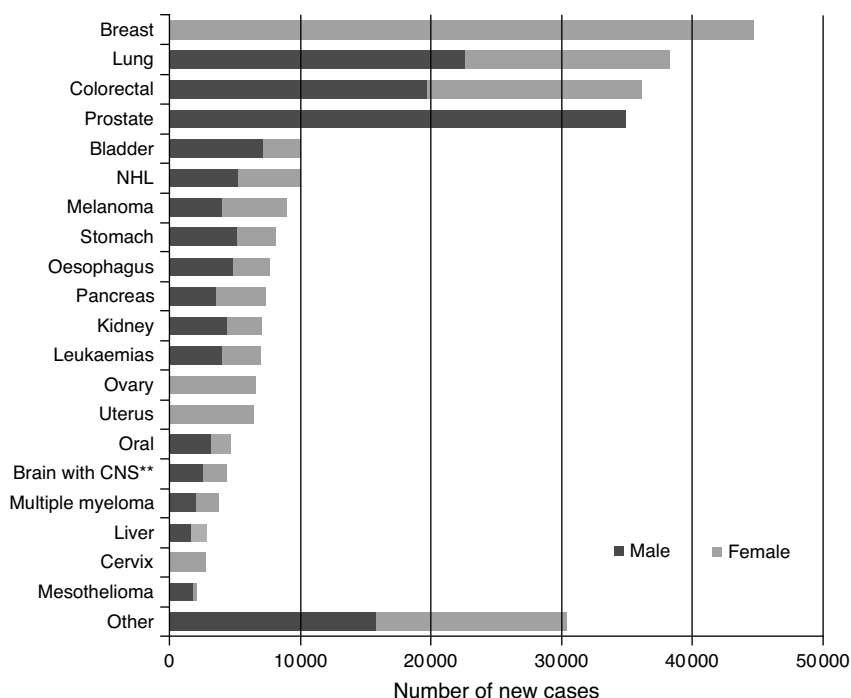
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1

Cancer epidemiology

1.1 Cancer incidence, prevalence and mortality

Every year, more than 285 000 people are diagnosed with cancer in the United Kingdom, and the current estimate is that more than one in three people will develop a form of cancer at some point in their lifetime. There are more than 200 different types of cancer, but four particular tumour types: breast, lung, colorectal and prostate-constitute over half of all new cases diagnosed (Figure 1.1). Cancer incidence, defined as the number of new cases arising in a period of time, is gender and age specific. In males, prostate cancer is the most prolific, where almost 35 000 new cases were diagnosed in 2004, followed by lung cancer, with around 22 000, and bowel cancer, with around 20 000 new cases per year. However, in females, breast cancer continues to be the most common tumour type, the disease accounting for nearly one in three female cancers, with over 44 000 new cases diagnosed in the year 2004. Cancer incidence may be further defined by the lifetime risk of developing the disease. For instance, in females, the risk of developing breast cancer is 1 in 9, and in males, the risk of developing prostate cancer is 1 in 14. In some tumour types, there are considerable gender-related differences in cancer risk; for example, males are nearly twice as likely to develop lung cancer (1 in 13) than women (1 in 23). Cancer occurs mostly in older people, and the risk of developing cancer increases with age. For example, in the 25–34 age group, the rate of diagnosis in males is 1834 cases per 100 000 of the population, and in females, 2782 cases per 100 000. However, in the 75+ age group, the rate of diagnosis in males has risen sharply to 52 831 cases per 100 000 in males and 50 803 cases per 100 000 in females. Overall, in the 10 year period 1995–2004, cancer incidence rate has been relatively constant, with a slight increase of around 1% in males and a slight increase in females of 3%. Broken down by cancer type, the largest increases in incidence rate within this period have been seen in malignant melanoma (43%), uterine (21%), oral (23%) and kidney cancer (14%). Cancer is currently the cause of a quarter of United Kingdom deaths, and around two thirds of all deaths in adults under 65 years. In fact, cancer caused 27% of all deaths in the United Kingdom in 2006; that is 29% in males and 25% in females. Five particular tumour types: lung, colorectal, breast, prostate and oesophagus, are responsible for over half (52%) of all cancer mortality (Figure 1.2). Survival is usually defined as the



** central nervous system

Figure 1.1 The 20 most commonly diagnosed cancers diagnosed in the United Kingdom, 2004. NHL, non-Hodgkin lymphoma. Reproduced with permission from Cancer Research UK <http://info.cancerresearchuk.org/cancerstats> August 2008.

percentage of patients diagnosed with cancer still alive after a 5 year period. Survival rates vary according to cancer type (Figure 1.3), where cancers may be grouped into three survival bands: 50% or higher, which includes testicular (95%), female breast (77%) and cervix (61%) cancers; 10–50% survival, including colon (47% in males, 48% in females), renal (45% in males, 48% in females) and brain (12% in males, 15% in females); and cancers where less than 10% of all patients are alive after 5 years, notably oesophageal cancer (7% in men, 8% in women), lung (6% in men, 6% in women) and pancreatic (2% in men, 2% in women) cancers. In general, women have higher survival rates than men (43% in men compared to 56% in women), and among adults, survival decreases with increasing age (Table 1.1). This may be due, in part, to mortality that is non-specific to the disease. However, other factors may be contributory, such as the smaller proportion of elderly patients entered into phase I clinical trials. Exceptions to this trend usually occur where the age of the patient at diagnosis is a reflection of the molecular and pathological characteristics of the tumour, for example, breast tumours in premenopausal women tend to be more aggressive, therefore survival rates in these age groups are decreased relative to postmenopausal women.

Progress in the early diagnosis and treatment of cancer has positively affected cancer survival rates. In the United Kingdom, female breast cancer mortality rate has fallen

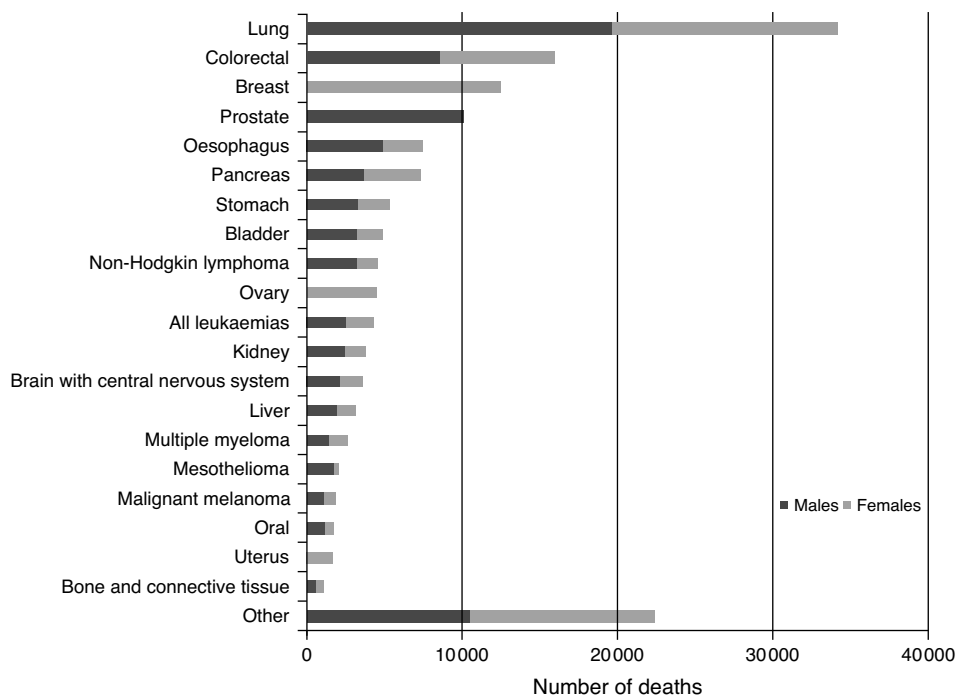


Figure 1.2 The 20 most common causes of death from cancer, persons, United Kingdom, 2006. Reproduced with permission from Cancer Research UK <http://info.cancerresearchuk.org/cancerstats> August 2008.

sharply, from 15 625 deaths from the disease in 1989 compared with 12 319 deaths in 2006. It is estimated that the National Health Service mammography breast screening programme saves around 1400 lives annually, detecting around 14 000 new cases of breast cancer per year. In prostate cancer, where tests for the biomarker prostate-specific antigen (PSA) have increased the proportion of PSA-detected asymptomatic prostate tumours diagnosed, and because these have an inherently good prognosis, the recorded survival rate has also increased dramatically. This is reflected by the change in 5-year survival rates over the period 1986–1999 (Figure 1.4), where the survival rate for breast cancer increased by an average of 5.4%, and for prostate cancer, by an average of 11.4% every 5 years.

1.2 Childhood cancers

By the age of 15 years, 1 in 500 children will be affected by childhood cancer, which in the United Kingdom means that around 1500 children are diagnosed with cancer every year. Childhood cancer is still relatively infrequent – the most common form being acute lymphoblastic leukaemia, though some rarer cancers are of embryological origin, such as retinoblastoma, rhabdomyosarcoma and neuroblastoma. Together, these were