

Medical oncology

OUR KNOWLEDGE OF THE biology of cancer has increased exponentially in the past 30 years. Although application of this knowledge to patient care has been modest, some important improvements in healthcare delivery are available now or expected in the near future.

Prevention. The prevention of cancer through dietary or drug interventions is a critical but largely unmet challenge. Recent clinical trials have shown that drugs such as the non-steroidal anti-inflammatory agent sulindac can reduce the size and number of adenomas in individuals with familial adenomatous polyposis.¹ Tamoxifen and the newer selective oestrogen-receptor modulators have similar benefits in breast cancer.¹ Yet, cancer chemoprevention is in its infancy, and issues regarding dosage and long-term treatment risk are unresolved. Finally, control of *Helicobacter pylori* infection may lead to lower rates of gastric cancer.

Diagnosis. Advances in cancer knowledge and genomics allow predictions of familial predisposition to several tumours, including breast, ovarian and colon cancer. The accurate diagnosis of familial cancer involves input from various medical practitioners, and increasingly involves recognition by pathologists of distinctive cancer phenotypes, such as breast cancer with *BRCA1* mutations or colorectal cancers seen in hereditary non-polyposis colorectal cancer.

The identification of germline mutations that cause colorectal or breast/ovarian cancer is both labour- and time-intensive. However, identification of these mutations facilitates screening of family members and the targeting of strategies for prevention or early detection of cancer, and allows reassurance of unaffected individuals within a cancer-prone family.

Intervention. Incremental advances in treatment modalities, including cytotoxics, hormonal agents and anti-emetics, have yielded modest improvements during the past five years. Sadly, of the more than 480 cancer therapeutics currently in clinical development,² few novel cancer treatments will reach the oncology clinic, and even fewer will have significant effects on cancer care.

For decades, we have been promised drugs that will target cancer cells without damaging normal cells, be they “magic bullets” based on monoclonal antibodies, or, more recently, “silver bullets” — small molecules that target genetic events central to carcinogenesis. In the past year, the clinical utility of some of these new therapies has been realised.

Two genetically engineered antibodies, trastuzumab and rituximab, are now available for treating breast cancer and non-Hodgkin's lymphoma, respectively. Their effectiveness results from targeting molecules important for tumour

growth rather than from immune-mediated cell killing. Trastuzumab targets the erbB-2 (HER-2/*neu*) receptor, which is overexpressed in about 20% of breast cancers, and antibody binding culminates in cell-cycle arrest.³ Trastuzumab is well tolerated, although it must be administered regularly to control tumour growth. One study has shown that the combination of trastuzumab and paclitaxel modestly improves the survival of women with advanced breast cancer. However, trastuzumab cannot be used safely with all chemotherapy, as illustrated by the high incidence of cardiac dysfunction (27% of patients) when the drug was combined with anthracyclines.

The “silver bullets” target fundamental genetic changes in tumour cells. One example is ST1571, a small molecule that inhibits the tyrosine kinase activity of the BCR-ABL fusion protein.⁴ This oral drug shows great promise for treating chronic myeloid leukaemia, reversing the haematological and cytogenetic features of the disease.⁵ It may also be effective against gastrointestinal stromal tumours owing to its activity against the tyrosine kinase KIT. This is particularly encouraging, as

these tumours rarely respond to chemotherapy and radiotherapy.

As drugs can now be tailored to specific molecular targets, there is a demand for complex molecular assessments of each tumour. For example, suitability for trastuzumab therapy is predicated on accurate identification of erbB-2 overexpression. This requires specialised, expensive techniques such as immunostaining and FISH analysis. This trend is likely to continue.

Up to 200 new anticancer drugs will be launched by 2005. These drugs will increasingly utilise our knowledge of the molecular basis of cancer. It is hoped that many of these drugs will act against malignancies of the lung and colorectum, for which there remains a large unmet clinical need.²

Robyn L Ward,* Nicholas J Hawkins†

* Medical Oncologist, St Vincent's Hospital, Victoria Street, Darlinghurst, NSW 2010, and Associate Professor, School of Medicine, † Senior Lecturer, School of Medical Sciences, University of New South Wales, Sydney, NSW
r.ward@garvan.unsw.edu.au

- Hong WK, Spitz MR, Lippman SM. Cancer chemoprevention in the 21st century: genetics, risk modeling, and molecular targets. *J Clin Oncol* 2000; 18: 9S-18S.
- Datamonitor Healthcare Reports. Cancer drugs of tomorrow: A quantitative pipeline analysis to 2005. London: Datamonitor Press, 1999: 26-70.
- Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001; 344: 783-792.
- Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med* 2001; 344: 1031-1037.
- Goldman JM, Druker BJ. Chronic myeloid leukemia: current treatment options. *Blood* 2001; 98: 2039-2042. □