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Cancer drugs – the economic challenge

Karol Sikora assesses the extent to which health technology assessments, the ageing population and societal changes will influence the future of cancer care

Cancer care costs are spiralling out of control in every healthcare environment. Ageing populations are ‘consuming’ healthcare in vastly increasing quantities. And new technology – drugs, devices and procedures – is increasing the cost of care. At the same time, top-up payments are increasingly used to break treatment-access barriers. In such an environment, cancer patients are beginning to become very sophisticated consumers of clinical services.

How much we are willing to pay for an extra year of good quality life is a key consideration for cancer patients of the baby boomer generation. For healthcare providers, the question is “how should people be asked to contribute to their care in an equitable way?”

Consumerism and social solidarity are not comfortable companions. In the UK we are now impinging on the very core of National Health Service (NHS) doctrine – free healthcare provided on the basis of medical need, not patients’ ability to pay. And for BUPA, the UK’s largest private medical insurer, oncology costs rose 140% between 2001 and 2006. Similar stresses are now emerging in other countries. Cancer care costs are likely to increase dramatically over the next five years driven by the factors described in Box 1.

It is likely that by 2012, we will see an above 200% increase to today’s costs in caring for cancer patients. In the short term, key cost drivers will include the signal transduction inhibitors and monoclonal antibodies that are approved in the US over the next 1-2 years and (as is often the case) in the EU several months afterwards. Supplementary New Drug Applications (sNDA) are being sought for drugs already marketed, both as line extensions for different cancers and for adjuvant use in early-stage disease. In addition, there are many more compounds, at least 500, in early-stage clinical trials that have not been issued with a generic name.

Other groups of cancer drugs that could receive an NDA approval within the next five years include: cancer vaccines; immuno-modulators; epothilones; HDAC inhibitors; gene therapy – antisense strategies; DNA repair inhibitors; and cell cycle inhibitors.

cost-reduction strategies

Efficiency gains

In future, cancer services will be rigorously reviewed for the value they offer. Given that the costs of cancer care are expected to escalate, it is vital to understand how we can make cancer services more efficient so that we can afford to deliver innovation.

A recent report providing an economic analysis of cancer care costs per head of population identified the UK as one of the highest spending countries in the EU at €200 per capita in overall cancer care but one of the poorest for cancer drug usage (see Figure 1).¹ Yet in the UK access is totally inequitable. That top-up payments are becoming more frequent implies huge inefficiencies in the delivery of care through the NHS. There are also huge variations in spending on cancer by each Primary Care Trust (PCT), ranging from £40-140 per person. With a total of 152 PCTs, some of this variation must reflect the demographics of the local population, but almost certainly attitudes to funding high-cost, low-efficacy cancer drugs are also at play. Compare this with the situation in France, which spends only €180 per head in total, yet has consistently managed to provide its population with speedy access to new drugs.

Better companion diagnostics

Until now, diagnostics have been under-researched because they offer relatively lower financial rewards compared with therapeutics. But today the use of companion diagnostics (see Table 1) to

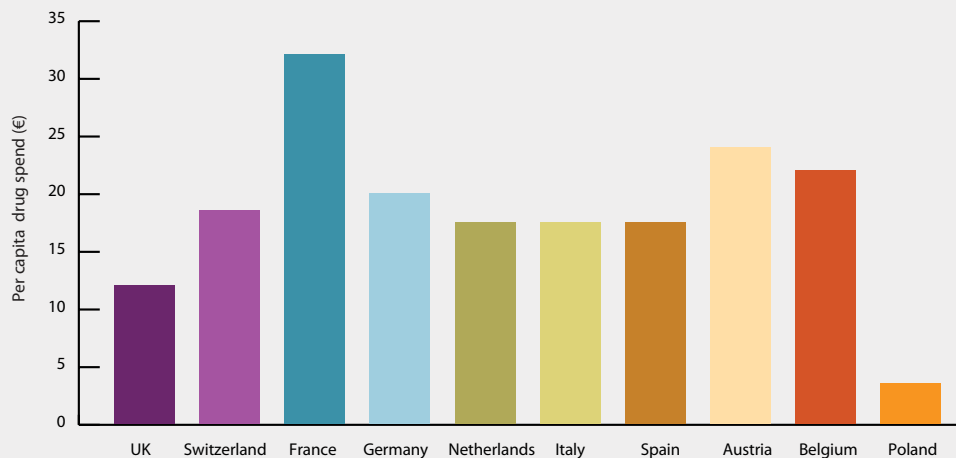
Box 1: Drivers of escalating cancer care costs

- New molecules obtaining an NDA in the US and priced at a premium.
- Continuing use of cytotoxics, with the attendant costs of side-effect management.
- Effective second-, third- and even fourth-line agents for common cancers.
- Increased use of drugs off-label.
- Increased cancer incidence and prevalence as survival improves.
- Increased costs of managing co-morbidities in elderly populations.
- Increased patient and carer demand.
- Increasing litigation including judicial review of negative funding decisions.
- Increased political pressure to raise the cost per quality-adjusted life year (QALY) limit for cancer.
- Pharma targeting patients through story placement by PR agencies.

Table 1: Diagnostics and cancer drugs

Diagnostic	Value
Predisposition screen	Identify patients for chemo-prevention
Screen for presence of cancer	Increase in patients – earlier disease
Pharmacodynamic biomarker	Establish pharmacological dose
Surrogate marker of clinical efficacy	Early indication of proof-of-concept
Predictive reclassification of disease	Target therapy to those likely to respond
Patient-specific toxicity prediction	Avoid adverse events, adjust dose

Figure 1: Oncology drug expenditure across selected European countries



Source: IMS Health

personalise care is becoming a useful approach for improving the cost-effectiveness of cancer drugs.

Key to reducing overall costs is the development of predictive strategies that allow the right drug to be given to the right patient. As the molecular mechanisms of most of the drugs currently in development are known, developing clinical tools to examine their likely effect on downstream pathways and predicting responses should be a natural extension of the tissue analysis carried out by pathologists. Such molecular signatures should increase the cost-effectiveness of any drug, however expensive.

Figure 2 examines the future discovery-to-development process driven not only by the drug itself but also by the ability to devise and implement pharmacodynamic endpoints, surrogate biomarkers and tissue markers predictive of response.

new drugs at this year's ASCO

The American Society of Clinical Oncology (ASCO) conference has become the yearly showcase for the cancer drug industry. How many new molecules will have moved forward enough to be presented in Chicago this May-June is a closely guarded secret. Indeed the Wall Street financial regulators have insisted on a single publication date in mid-May this year to prevent insider dealing on US biotech stocks. A review of last year's abstracts identifies 21 small molecules and 16 monoclonal antibodies that have been given generic names. We can therefore estimate that at least around 10 new drugs will reach the marketplace during the next 12 months and around 30 by 2010. These drugs are not likely to reduce costs elsewhere in cancer care.

Near simultaneous submission to the regulatory authorities in Washington, London and Tokyo – representing the three largest pharma markets – is becoming more common, and this means less and less lag time between marketing in the EU and the US. This is important because strategies for cancer drug development have become increasingly commercial, involving: increasing speed to market; increasing speed to peak sales; lifecycle management – late metastatic, early metastatic; adjuvant, prevention; and generic defence.

This puts huge and often unsustainable pressure on the global payers of healthcare whatever type of insurance system is being used, be it tax based, social or private insurance or a Health Maintenance Organisation.

the grey vote

The majority of cancers occur after the age of 65. The growing political power of old people in democracies is sure to have an increasing impact on the provision of cancer care. More people will be living longer and their chronic health problems will not necessarily incapacitate them physically or mentally. This educated gerontocracy will have high expectations, sharpened through the first two decades of the 21st century, and they will not tolerate the standards of care offered to many old people today. They will wield considerable influence. So will a tax-based health system be sufficient to fund their expectations?

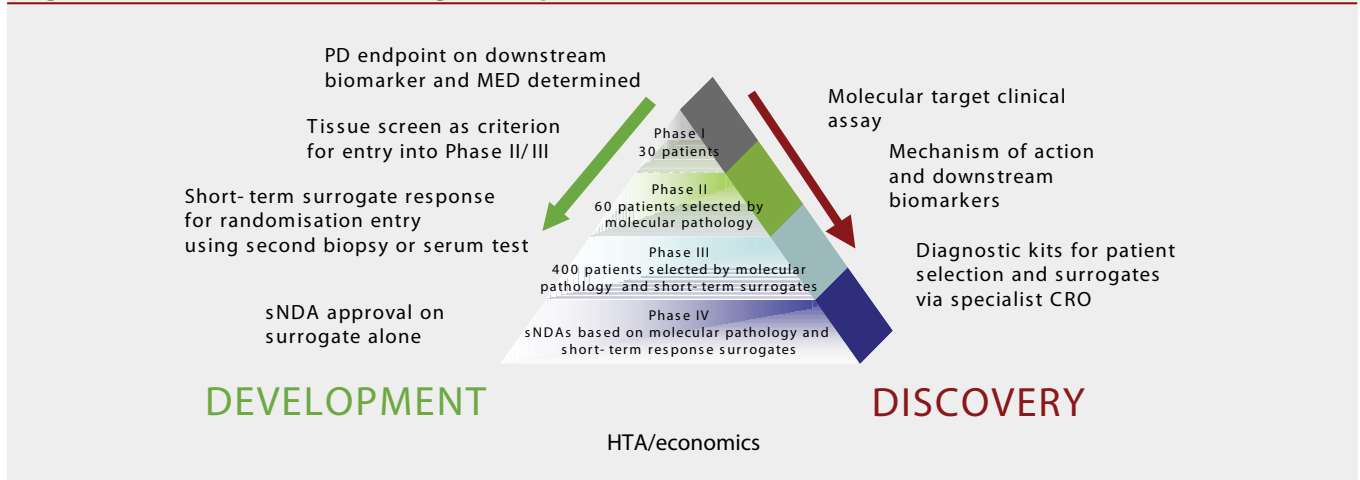
Politicians will have to consider the alignment between patients' requirements, and taxpayers'/voters' wishes. Fewer than 50% of voters in most countries now pay tax, and the percentage of tax-paying voters is set to fall as the population ages. Will the younger taxpayers of the future tolerate the expensive wishes of non-taxpayers? The interests of voters may be very different to the interests of taxpayers. It seems likely, therefore, that the days of an exclusively tax-funded health service are numbered.

Whatever system is put in place, there is the prospect of a major socio-economic division in cancer care. A small percentage of the elderly population will have made suitable provision for their retirement, both in terms of health and welfare, but the vast majority will not be properly prepared. Hence policymakers need to start planning for healthcare now just as they are doing for the looming pensions crisis. The most productive way forward is to start involving cancer patient and health advocacy groups in the debate, to ensure that difficult decisions are reached by consensus.

care at what price?

New financial structures are likely to emerge with novel consortia from the pharmaceutical, financial and healthcare sectors enabling people to buy into their chosen level of care. Cancer, cardiovascular disease and dementia will be controlled and join today's list of chronic diseases such as diabetes, asthma and hypertension. Hospitals will become attractive "health hotels" run by competing private sector providers. Global franchises will provide specialty therapies through these structures in a similar way to the internationally branded shops found in today's malls. Governments will soon cease to attempt to deliver care.

Figure 2: The future of cancer drug development



The ability of technology to improve cancer care is assured. But this will come at a price – the direct costs of providing it and the costs of looking after the increasingly elderly population it will produce. We will eventually simply run out of things from which to die. New ethical and moral dilemmas will arise as we seek the holy grail of compressed morbidity. Living long and dying fast will become the mantra of 21st century medicine.

Our cancer future will emerge from the interaction of four factors: the success of new technology, society's willingness to pay, future healthcare delivery systems and the financial mechanisms that

underpin them. The future of cancer drug discovery and development will from now on be dominated by health technology assessment and economics.

References

1. B Jonsson and N Wilking, 'A global comparison of access to cancer drugs', *Ann Oncol*, 18 supp 3:1-80, 2007.

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DR JOHN WHITTAKER

Targeted thinking

Dr John Whittaker talks Scrip through the unique challenges and opportunities that define the oncology landscape

Q How does clinical research in oncology differ from other therapy areas?

There are far more drugs in development for cancer than for any other disease and many more innovative first-in-class drugs with novel mechanisms of action and targets. Oncology has a unique terminology requiring a clinical team with expertise to understand its complexities.

Clinical research in oncology requires expertise in designing drug development plans, from planning and project management of individual studies within programmes to estimation and management of risk and go/no-go decision points.

Site selection for oncology trials is now an advanced science, requiring a precise understanding of the patient group of interest in addition to knowledge of the local regulatory environment and clinical practices in each country.

Q How has the oncology landscape changed in recent years?

- Use of biomarkers to measure pharmacokinetics and drug action and patient response is an increasingly necessary aspect of many clinical trials.
- Most CROs are routinely utilising adaptive methods in their clinical trials.
- To an increasing extent, go/no-go decisions need to be made by developers of new therapies with an eye toward the eventual pricing of the agent and its value to the medical community.
- With the advent of "targeted therapies," selection of the appropriate study endpoint is critical to success.

Q What insights can Kendle share from its clinical experience in oncology?

Drug development is about creating an integrated development landscape that takes new therapeutic agents from the bench to the clinic. Personalised medicine in clinical practice is the end goal, but validating genetic markers that correlate reliably with clinical outcomes across patient groups and geographies can be a struggle. Personalised medicine is about the patient, and this is what drug developers and CROs need to be about too.

Q How does geography affect recruitment of cancer patients?

It is estimated that 85-95% of clinical trials

experience delays beyond one month. The most common reason for delays is poor patient recruitment.

Recently we have seen a shift in patient recruitment away from North America and Western Europe toward developing regions. Not so long ago, it may have been possible to realistically anticipate recruitment rates from North American and Western European sites of one to two oncology patients per site per month or even higher depending on the tumour type. For more common tumour types, it is now more prudent to work with lower expected rates of 0.1-0.5 patients per site per month in these regions.

Q What are the most promising new technologies in oncology?

Molecularly-targeted drugs have emerged, providing hope for improved efficacy and reduced side-effects. However, the number of tumour types addressed by newer agents is still modest, so the market for supportive care products to treat the side-effects of chemotherapy continues to grow at a significant pace. Targeted therapies, such as monoclonal antibodies and oral tyrosine kinase inhibitors, will be used in most cancer patients in five to 10 years.

Many agents act on targets involved in cell signalling, and more recently, angiogenesis, but now we are starting to see more targeted inducers of apoptosis and inhibitors of metastasis. CROs are looking carefully at appropriate study designs for clinical trials that take into account (and indeed help define) mechanism of action.

Cancers that previously were chemotherapy-resistant are now showing tumour responses and improvement in overall survival. From pharmacodynamic biomarkers that give proof-of-mechanism and/or proof-of-principle, biomarkers are proving to be valuable tools as surrogates for efficacy. As we progress toward personalised medicine, we expect to see more diagnostic kits using patient selection biomarkers. There are various examples of circulating tumour cells being used as biomarkers in oncology drug studies. Imaging technologies (PET, MRI and CT scans) are now used for quantitative analysis and as clinical trial endpoints.

Q How significant are companion diagnostics used alongside therapeutics?

It is no longer acceptable to provide the same treatment to all patients. Accurate, validated

diagnostic kits employing biomarkers that identify susceptible patients are essential adjuncts to such trials and need to be developed and validated to permit the conduct of such studies. With the advent of molecularly-targeted therapies, we will see many more trials involving designs that enrich for patients with a tumour gene profile likely to benefit from treatment with the study agent.

Q Are cancer care costs sustainable?

There is unmet medical need for less toxic cancer therapies and a need for drugs with improved tumour selectivity. With products costing more than \$10,000 annually, balancing medical demands against treatment costs is an issue in all developed countries. It is always difficult to make a case for treating a few individuals with an expensive therapy vs. many people with cheaper medication, but our industry must continue to emphasise the benefits to society of treating those few.

Q What do you think about the societal challenges posed by cancer?

It's more than just cancer. Society needs to find ways of caring for and treating a growing population with a wealth of age-related chronic conditions, including cancer.

In the short-term, the best hope for patients in need of treatment with expensive novel agents is that exceptions can be made to prescribing rules. The option for patients to pay for part of their National Health Service care should be permitted.

Q What do you think about Karol Sikora's model for the future of cancer drug development (on page III)?

Professor Sikora elegantly captures the new model for cancer drug development and provides optimism for future cancer patients. One of the challenges for drug developers and clinicians is to identify novel ways of combining agents together rationally (or with conventional therapy) to treat sub-groups of patients and ultimately individuals likely to respond to such agents.

Dr John Whittaker is Director Global Clinical Development at Kendle.



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There is much more work to be done and we can't do it alone. That's why we're always seeking those who share our belief that science can improve our world, that by working together we can bring promising new therapies to patients on a global scale.

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