New drug treatments for cancer: what the future holds

DANNY BUCKLAND

Cancer drug research is a rapidly expanding field, with thousands of new products in active development. Danny Buckland discusses how innovative new cancer treatments coming to the market and the associated financial pressures will impact on the NHS and patients in the UK.

The headline figures from the oncology drugs pipeline look like a sabres-drawn cavalry charge that will sweep all before them. The statistics are impressive – 6484 products in active development across a range of novel mechanisms that can thwart cancer’s most malevolent mutations and variations.

More than 2000 of these are first-in-class – according to the GBI Research’s *Frontier Pharma: Versatile Innovation in Oncology* report1 – as scientists get the upper hand in cracking genetic coding to deliver innovative disease-modifying therapies.

Almost a decade of development following the first cancer genome sequencing report in 2006 has elevated the treatment of cancers to unprecedented levels of success. Clinicians now have a formidable arsenal to combat cancer from small molecule inhibitors to cure-delivering immunotherapies.

The library of effective drug combinations is growing and, combined with a more muscular use of data, therapies can be targeted and stratified to promise enhanced survival and quality of life for cancer patients.

Ambition is in the air. Cancer Research UK has recently invested in a Cambridge laboratory looking for antibodies against specific drug targets and it has launched a Grand Challenge to find ways of “drugging the undruggable” such as the Myc gene, which is an accelerant in a significant number of cancers.

The potential suggests a fast approaching “And they all lived happily ever after” moment but, despite the genuine medical triumphs, discovery and delivery seem to run on different tracks and misconnecting timetables.

As the consultation period for a recalibrated Cancer Drugs Fund (CDF) closes on 11 February, it is timely to ask if the trumpet-bla ring is a little too soon and if the pipeline force will be reduced to a trickle by the time the patient is involved?

Cost-benefit issues
Simon Stevens, Chief Executive of NHS England, has already sounded a note of caution by stating: “Over the next five years
we’re likely to see many new cancer drugs coming on to the worldwide market – some of which will be major therapeutic breakthroughs, and some of which will turn out to offer little extra patient benefit but at enormous cost.”

The cost-benefit argument has been raging for some time with the pharmaceutical industry and government regulatory bodies propounding switchback views at times. A restructured CDF will aim to strike a balance but it is a tightrope walk teetering between dire financial pressures on NHS funding and the pharmaceutical industry’s lament that a new drug costs £2.6 billion and a decade to develop.

The cancer landscape will not provide a soft landing. There are 2.5 million people in the UK with cancer and 300 000 new cases are diagnosed and 161 823 deaths registered each year, according to Cancer Research UK’s latest figures. The UK experiences 10 000 more cancer deaths than the European average with 5000 of those as a result of late diagnosis. Demand is surging upwards while NHS funding is heading in the opposite direction.

An indication of the degree of difficulty facing the NHS and NICE hit home in October when the lung cancer drug nivolumab, which is proven to be twice as effective as chemotherapy in clinical trials, was rejected because its £100 000 per person price tag for a year of good-quality life was deemed too expensive. NICE also rejected the breast cancer treatment Kadcyla (ado-trastuzumab emtansine) because it cost £90 000 a year.

NICE will play an even more important role in a revamped CDF as it will be expected to make rapid “yes”, “no” or “maybe” rulings on new drugs. The “maybe” element will be hard-chiselled but is likely to offer a conditional approval of expensive drugs while data is collected over a two-year period to allow more-informed data-driven decisions.

“It is true that the increasing strain on NHS resources is a very strong pressure, especially when the benefit of the drug is marginal. Kadcyla provides a few months extra survival over Herceptin so it wasn’t deemed acceptable,” says Dominic Trewartha, a senior analyst at GBI Research. “Those are the cold figures but when you are in a clinic, these drugs that provide an extra three months or maybe a year are very meaningful so obviously there is a huge tension between healthcare providers, NICE and pharmaceutical companies.”

Challenges facing the NHS and NICE
The stakes are high. By 2032, 61 per cent of the population will be over 65 years and in some areas of the country 1 in 10 people will be aged over 85 years. The bill to treat them can only rise and the Institute for Healthcare Informatics reported that the global spend on all oncology drugs burst through the $100 billion barrier last year.

The pharmaceutical industry believes it is playing its part and demonstrated that commitment with a pledge in December 2015 to pump £550 million into the NHS economy during 2016 as part of the Pharmaceutical Price Regulatory Scheme, started in 2014, to make it easier for new and innovative medicines to reach the patient.

But at a local level, the impact of rising drugs price tags is graphic. Steve Williamson, a consultant pharmacist for cancer services at Northumbria Healthcare NHS Foundation Trust and a former CDF panel member, observes: “As technologies have developed and we have more innovative cancer drugs, the average cost of a course of treatment has risen exponentially. About 10 years ago it was £10 000 and it is now approaching £30 000 to £50 000.

“The number of people we have to treat for cancer is rising because we have an ageing population and treatments have increased because patients have more lines of chemotherapy so not only has the time they are on cancer treatment increased but so has the volume. This is good news for patients because they are living longer but the cost increases.

“I work at a busy Trust with 500 000 patients and we cover common cancers. We are not a specialist centre yet our chemotherapy budget over last 10 years has gone from between £100 000 and £200 000 up to £10 million and we are not treating fantastically more numbers of patients. Think about that level of growth and what else has gone up that much in a corresponding time?

“It is down to pricing; 15 years ago we had traditional chemo drugs and would consider it expensive to spend £300 to £400 a month on a drug. We are now looking at £5000 a month for new drugs coming on line which, although they are promising a lot more, don’t work for everyone and you cannot necessarily identify the patients they will work for.”

The human jeopardy in any medical economics discourse is obvious and the malignant melanoma immunotherapy drug ipilimumab characterises the fundamental issues at stake. It costs around £90 000 per patient and, for eight out of 10 patients, it provides three to four months extra life. “That doesn’t seem worth it,” adds Mr Williamson. “But two out of every 10 get a much better outcome. We still have to pay for eight of the 10 who don’t get that extra.”

Early access schemes and risk sharing can defray the costs for the financially challenged NHS but new thinking is needed to provide clinicians with a sustainable and enduring system to work with. The NHS England pledge is for sharper decision
making – NICE will be committed to a 90-day turnaround – in the redrawn cancer strategy.

“There will be challenges for NICE. It does not have a history of being able to make timely decisions and this will mean every drug will have to be looked at quickly,” says Mr Williamson. “The pharmaceutical industry will have to co-operate by providing timely data. But at the CDF, we discovered that the UK price of a drug was not always known until just before it was marketed, which would be too late for NICE so there is a question mark about how it will be able to rule without a timely indication on price.

“Oncologists have been generally happy with CDF, although it was a sticking plaster solution. With the huge funding gap, the NHS could not afford to keep topping up the CDF at the expense of other treatments. Against this backdrop, we are faced with the clinical dilemma of seeing these exciting drugs being used in other countries yet we cannot use them.”

**Impact on patients**

Patient groups are dismayed by recent decisions, and the confusion among members of the public, who can research fine detail about breakthrough drugs online but not receive them in the GP surgery, is palpable.

Dr Sarah Jarvis, a practising GP and media broadcaster, believes the lack of clarity has a corrosive side-effect on the physician-patient relationship.

“It endangers that relationship and not just in terms of cancer drugs,” she says. “Time was when a patient came in to see me and would automatically assume my only interest was in what was best for them. Now they ask if there is something better that I could offer that I’ve not told them about because I am trying to save money – that question comes all the time.

“There has been a shift from patient responsibility to entitlement and the reaction doctors often get is: ‘I know that drug is expensive but I should have it’. They genuinely do not believe there is anything wrong with that standpoint. This will continue to be a real challenge.”

The CDF, which had a £340 million budget in its final year and helped 72 000 patients during its lifetime, has been besieged by controversy as cold, hard clinical and financial decisions to cut drugs from its approved list were made in an arena white hot with emotion. Blocking a chance of a life-enhancing drug from a group of terminally ill patients is rarely judged by logic alone.

Paula Chadwick, the chief executive officer of the Roy Castle Lung Foundation, is critical of the ruling and the pricing on nivolumab. “I’ve been working for this charity for 20 years and this is the first significant breakthrough we have had and the price issue is frustrating,” she says. “We all know the NHS cannot fund everything but if we are saying, as the National Cancer Strategy states, that we should have first-class cancer outcomes then we have to have a process that gives an option to fund them otherwise we will continue to lag behind. The UK has the worst lung cancer survival rates in Europe and, if we can’t fund new drugs, how can we improve those statistics?

“We cannot have the situation where effective drugs are not available in the UK. That is not good for the patient or the manufacturer. Nivolumab would make a significant difference to some patients’ lives but they are being denied it, which is frustrating for both the patients and the clinicians and oncologists who are not able to prescribe a drug they know will make a difference.

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**Reaching unmet need**

NICE also came under fire for refusing Abraxane (paclitaxel albumin) to treat pancreatic cancer because it did not provide enough extra life under the regulatory body’s quality-adjusted life year (QALY) assessment even though it was at a much lower price tag than other drugs that have been refused.

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“Abraxane was the first to show a significant survival in 17 years, which is a very long time. It is not just two months, some outliers are surviving beyond two years, but patients cannot get it because of the funding system, although you can get it in Scotland and Wales,” says Ali Stunt, founder of Pancreatic Action Group. “I could understand if it was going to be costing £100 000 a year but we are looking at cost per patient of £5000 to £8000. This is not about price – it just doesn’t fit the NICE QALY threshold – an average 2.1 months is not enough to clear the hurdle to make it cost effective to the NHS.

“It is clear that we need more innovative drugs to be approved and we need all interested parties discussing it, and the pharmaceutical companies need to do their bit. There should also be a separate method of calculating the value from drugs that reach unmet needs. A ‘one-size-fits-all’ approach is not working and will not help us move the numbers for pancreatic cancer.

“A recent study, conducted by Celgene, discovered that oncologists can be reluctant to discuss treatment options that are not readily available, so they are not giving the whole picture out of a desire to protect the patient by not describing what they can’t have. They want to give the best treatments but feel their hands are tied over what they can prescribe. This can degrade the relationship between patient and physician.

“It is always worth discussing all options. The system, particularly with regard to pancreatic cancer, does not seem fair to patients and clinicians.”

**New ways of assessing value**

Industry experts believe there should be a fresh approach to a medicine’s value that encompasses a range of economic factors not currently assessed when deciding the cost of a new drug.

“It does look to be more exciting now with the promise of stratified and personalised medicine from a better understanding of genetics and disease to more accurately target treatments. The promise has been around for a long time but we are starting to see treatments that deliver against it,” says Richard Torbett, executive director – commercial UK of the ABPI, the trade body that represents companies supplying 90 per cent of medicines used by the NHS. “There’s also a lot of talk about the potential of immunotherapy, which is genuinely impressive.”

But he emphasises that understanding of the scale of investment needed to bring a medicine from bench to bedside is low and that the $1 billion development figure often cited has inflated to $2.6 billion. A return on that investment is an industry essential to sustain the research and development programmes that will continue to incubate novel medicines.

“The debate now is to understand the value of a medicine in a better way and to make sure we have good systems within the NHS so the pharmaceutical company and the system can have a sensible discussion about how much a medicine is worth and come to a good view to make sure patients get access,” he adds.

“There are many dimensions to the value for patients such as extending life and the quality of life, improving people’s ability to stay at home, and value in terms of allowing people to stay in work. There are many factors relevant to a fair debate about how we should assess medicines. Some are quite measurable, some of them less so and that is where you can get into difficulties.

“Our concern has not been to dodge the fair scrutiny of NICE, which is a really important part of the process, but do we think the NICE methods work for all disease areas? The answer we have had for some time is, probably not.”

Existing systems have allowed the UK to lag behind other countries on adopting new medicines but he sees hope with NICE at the centre of a reworked structure, providing any CDF replacement takes account of the broader aspects of cost and is not restricted by a definitive budget.

“The emphasis should not be on price but on how much value we are delivering to patients – do we think it’s worth it?” notes Torbett. “NICE has got an important role to play and as long as it is properly resourced and can take account of the unique characteristics of end-of-life care, it is good that the future of cancer is NICE-led. But that is not to say every medicine will get through. They are there for scrutiny.

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“**Innovative treatments**

Dr Kat Raney, Cancer Research UK’s science communications manager, is enthused by the growth of innovative medicines, which move away from the groove of small-step improvements in small-molecule therapies. Molecular diagnostics, using blood tests to pinpoint a cancer’s characteristics, will also make it
easier to choose the most potent combinations of drugs to treat tumours, she says, while a sharper focus on hard-to-treat cancers could generate significant gains.

“The pace of development is really accelerating and will only get faster,” notes Dr Raney. “But getting that through trials and through the regulations to patients is the key. We’ve already seen cancer survival double in the last 40 years and we have reached a stage where half of patients diagnosed today will survive for 10 years on average.

“People talk of a golden age and the field has certainly hotted up over the last five years in that we are seeing more targeting of drugs and we now have an abundance of data. It is now a question of how we use it, how we make best use of the drugs we have and how we look for new approaches.

“It is an incredibly exciting time. I lost my granddad to prostate cancer in the early ’80s when I was eight years old and it was just before hormone therapy when there was virtually nothing. We’ve seen the development of a whole array of new prostate cancer drugs and it is the same in many forms of cancer. Survival really is changing.”

Tellingly, she adds: “There is a lot of exciting stuff in the pipeline but it will be a challenge to work out who will benefit and a challenge for the health service to work out how they can afford it.”

Declaration of interests
See http://www.mjauk.org/author/bucklanddd/

Reference

Danny Buckland is a health writer and journalist

POEMs

Cognitive behavioural therapy vs light therapy for seasonal affective disorder

Clinical question:
How does cognitive behavioural therapy compare with light therapy for treatment of seasonal affective disorder?

Bottom line:
Cognitive behavioural therapy for seasonal affective disorder (CBT-SAD) provided to small groups of patients for 18 hours over six weeks is as effective as daily light therapy for the treatment of seasonal affective disorder. Even in group therapy format CBT-SAD would be more expensive. (LOE = 1b)

Reference:

Study design:
Randomised controlled trial (nonblinded).
Funding: Government.
Setting: Outpatient (any).
Allocation: Concealed.

Synopsis:
In this randomised controlled trial 177 patients with current diagnosis of seasonal affective disorder (SAD) were randomised to either CBT-SAD or light therapy. Participants were adult community volunteers recruited in autumn and winter months through local media in Vermont (44.5 degrees north) and referrals from health clinics.

Inclusion criteria were diagnosis of depression based on DSM-IV-TR criteria, a current SAD episode, and either no use or stable use of antidepressant medications. Participants were excluded if they were in current psychotherapy or light therapy, had prior light therapy or CBT for SAD, had serious mental illness requiring acute treatment (eg psychosis, suicidality) or hypothyroidism, or had plans to leave the area for more than one week during March. Allocation was concealed and outcome assessment was blinded. The six-week treatment period had to commence by the first week of February. Light therapy was with a source providing 10,000 lux of cool fluorescent light through an ultraviolet filter, started at 30 minutes daily in the morning and adjusted according to a protocol if needed. CBT was specifically tailored to SAD and provided in groups of four-eight participants by one of three therapists in two 90-minute sessions weekly for six weeks.

Dropouts were higher in the CBT group (13/88) vs the light group (1/89). Remission as assessed using two different tools, SIGH-SAD and BDI-II, did not differ between groups at the end of the study period. About half of participants in each group achieved remission. The proportion in remission difference between light therapy and CBT-SAD was small, but clinically insignificant (0.004 for SIGH-SAD and 0.076 for BDI-II).

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