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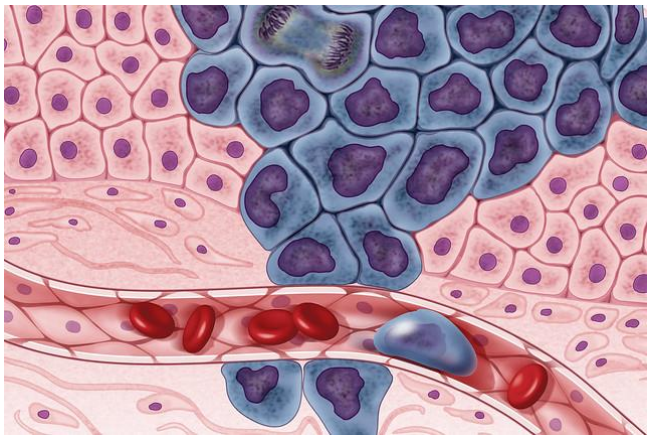
Advances in Cancer Treatment



The pace of innovation in cancer treatment is rapid, with promising developments for patients in terms of survival and quality of life. Research in the fields of immunotherapy and radiotherapy has shown positive results in treating some cancers where established treatments are not effective. This POSTnote gives an overview of recent advances, the potential benefits and risks, and considers the opportunities and challenges of using new technologies in the NHS.

Overview

- New cancer treatment technologies have shown promising results in clinical trials, particularly for difficult-to-treat cancers.
- Significant progress has been made in cancer immunotherapies for specific cancers and patient populations. Research into the use of these therapies for other cancers and patients is ongoing.
- Advances in radiotherapy include improved imaging and precision, proton beam therapy, and molecular radiotherapy, all with positive clinical results.
- Combination therapies, which combine different types of immunotherapy, or drug and radiotherapies, are a research priority.
- New therapies require specialised knowledge and resources. Stakeholders agree that they should be delivered as part of a comprehensive multidisciplinary care package.

Background

Cancer is the leading cause of death in the UK for both females (25.6%) and males (30.3%) when all cancers are grouped together (around 164,000 deaths annually).[1] Prevention of cancer is a public health priority, in part due to increased understanding about genetic, behavioural and environmental factors in causality and how to prevent them.[2] Technological advances mean that cancer treatment options are improving rapidly, and patients have better prospects, both in terms of clinical outcomes and quality of life. Cancer is a key area for ongoing improvement for NHS England in the NHS Long Term Plan (2019), which sets out its commitments for cancer prevention, diagnosis and treatment.[3] NHS Scotland and NHS Wales also have cancer strategies.[4,5] The Department of Health in Northern Ireland recently announced it will launch a similar strategy.

More people in the UK are being diagnosed with cancer than ever before, partly due to improved diagnosis and greater public awareness. There are more than 360,000 new cancer cases in the UK every year.[6] At least half of all UK citizens born after 1960 will be diagnosed with some form of cancer during their lifetime.[7] The rise in cancer diagnoses is also attributed to changes in demographics and patterns of chronic disease. An ageing population, unhealthy eating habits, lack of exercise and poor sleep patterns are predicted to cause a further 2% rise in cancer incidence by 2035.[8,9] However, cancer survival in the UK has doubled over the past 40 years, with half of people diagnosed surviving for 10 years or more.[10] Some cancers will become treatable as long-term chronic diseases as treatments improve.

Current Treatment Approaches

The current standard of care for cancer can involve a range of treatments, usually in combination.[11] This might involve a combination of surgery to remove tumours, chemotherapy and/or conventional X-ray radiotherapy to kill cancer cells. Standard treatments are highly effective in treating some cancers, such as breast cancer, prostate cancer and some types of leukaemia. Other cancers are more difficult to treat due to the location of the disease, its resistance to therapy, or the patient's general health.[12] These include tumours of the brain, lung, pancreas, oesophagus, head and neck, cancers diagnosed at a late stage, and those that have spread (metastasised).

While they are effective first-line treatments, chemotherapy and radiotherapy can cause serious side effects that impact on patients' quality of life.[13] For example, secondary cancers develop in around 5% of patients receiving conventional X-ray radiotherapy due to the irradiation of surrounding tissue.[14] Over the past decade, important progress has been made in "targeted" and "personalised" treatments.[15] Using advances in physics and engineering combined with new diagnostic capabilities and genome editing techniques, some treatments can now be tailored to specific patients and specific types of cancer cells.[16,17] This also means that patients for whom the treatment is unlikely to work will avoid unnecessary exposure to toxicity.

Recent Advances in Treatment

This note covers the following advances in specific treatment areas that have recently shown promising results in clinical trials (Box 1) and/or in clinical practice.

- **Immunotherapy**
  - **Chimeric Antigen Receptor T-cell Therapy:** engineers a patient's T-cells so they will attack cancer cells more efficiently
  - **Immune Checkpoint Inhibitors:** block immune cell mechanisms, releasing the "brakes" on the immune system so that it can better kill cancer cells
- **Radiotherapy**
  - **Proton Beam Therapy (PBT):** irradiates cancer tumours with a beam of protons (small parts of atoms)
  - **Systemic Radiotherapy:** involves infusing or injecting radioisotopes into the patient to damage cancer cells
- **Oncolytic Virus Therapy:** uses viruses to kill cancer cells and stimulate the immune response
- **Combined Approaches**

Box 1. The Clinical Trials Process

Treatment development is a multi-stage process carried out by academic research centres and, in the case of drugs, pharmaceutical companies.[18] Funding can come from government research grants, pharmaceutical companies and charities. Researchers at universities and research institutes normally carry out early stage lab-based research into the cell and molecular biology of cancer. New discoveries are tested for safety in animal models. Further large-scale trials are then carried out to test for clinical efficacy and safety in humans, usually conducted by pharmaceutical companies, who are developing a particular drug, or by clinical academic centres, in the case of radiotherapy.[19] Further clinical trials determine the ideal dosage or radioactivity; its use in different cancer types and different patient populations; and the potential for a treatment to be used instead of, or in combination with, existing approaches.

At present, there are around 700 clinical trials into cancer treatments in the UK, many of which are testing the effectiveness of combined treatment strategies.[20] Trial information is available through the UK Clinical Trials Gateway.[21] If successful in clinical trials, new treatments are assessed for clinical efficacy and cost-effectiveness by the National Institute for Health and Care Excellence (NICE) for use in the NHS in England and Wales.[22]

Overall, recent advances in treatment have demonstrated promising evidence of improvements in survival rates and quality of life for patients, and some improvements in side effects. Experts have cautioned that most of these treatments are approved as a second- or third-line treatment for specific cancers and patient subgroups. As they are trialled for different indications they may become first-line treatments. New technologies are generally more expensive than standard treatments and require highly skilled clinical staff and specialised facilities to deliver them.[23]

Immunotherapies

Cancer immunotherapy covers a range of technologies that use the patient's own immune system to damage or kill cancer cells. Most approaches involve adapting or engineering T-cells, a type of white blood cell that plays a key role in fighting infection and disease.[24] Cancer cells deploy various tactics to prevent T-cells identifying and destroying them. Immunotherapy research is focused on engineering the immune system to overcome these tactics. These therapies are for specific patient groups. They may require a particular gene to be present to function, and patients might need to be relatively healthy to withstand treatment. A treatment might only work on a specific form of cancer due to the varying ways the disease attacks healthy cells. These treatments can have severe side effects, detailed below. They are also expensive, particularly if they are personalised or genetically engineered treatments.

Chimeric Antigen Receptor T-Cell (CAR T-cell) Therapy

CAR T-cell therapy involves collecting, modifying and using a patient's own T-cells to treat their cancer. The biology of this process is complex (see Box 2). So far CAR T-cells have been highly effective in treating a number of blood cancers. Several hundred patients with B-cell leukaemia, B-cell lymphoma and myeloma have been successfully treated in clinical trials.[25] The first NHS patient was infused with CAR-T cells at Great Ormond Street Hospital in January 2019.[26] The associated clinical research team at University College London leads the European field in CAR T-cell research, with ten trials currently recruiting.[27] A meta-analysis of CAR T-cell therapy found that, 67% of blood cancer patients survived without disease progression for at least 6 months to 1 year.[28] A future goal is to have universal "off the shelf" CAR T-cell therapy, which would be more cost-effective for drug developers, and potentially cheaper to provide on the NHS.[29]

In 2018, NICE recommended CAR T-cell therapy for two patient groups through the Cancer Drugs Fund (CDF) (see page 4). According to current guidance it is not intended as a first-line treatment, but for patients for whom conventional chemotherapy is not effective.[30] A panel of clinicians makes decisions about individual patient eligibility. The treatment is now available on the NHS for the following patient groups while more clinical data on patient outcomes are collected:

- Children and young adults aged up to 25 years old with acute lymphoblastic leukaemia that has not responded to standard treatment approaches.
- Adult patients with certain types of lymphoma, if two or more previous therapies have failed.

CAR T-cell therapy can have severe adverse effects. Between 50–80% of patients who have undergone systemic T-cell therapy experience cytokine release syndrome (influenza-like symptoms and high fever) and some have neurological side effects, such as confusion.[31] Research is being carried out on injecting CAR T-cell infusions directly into tumours, for cancers that are localised rather than those that affect the whole body. A trial at King's College London has found that this approach is safe and demonstrates some slowing of tumour growth in patients with difficult-to-treat head and neck cancers.[32]

Box 2. How Does CAR T-cell Therapy Work?
T-cells have protein receptors on their surface that recognise fragments of protein (antigens) that are presented by other immune cells. When T-cell receptors detect these antigens, the T-cell "turns on", releasing toxic chemicals to damage the cell, and recruiting other immune cells to the area.[33] Cancer cells can disguise themselves as healthy cells and block this immune response.

In CAR T-cell therapy a sample of the patient's T-cells are modified in a laboratory. An inactive virus is used to introduce genetic information into the T-cell so that they produce receptors that recognise and attach onto cancer antigens. These cells–now chimeric antigen receptor T-cells–are stimulated to multiply rapidly and are infused back into the patient in a single treatment. The receptors allow them to locate and kill the cancer cells. Where therapy fails, it is usually because CAR T-cells do not persist long-term, fail to reach the tumour in sufficient numbers, or the cancer cells have evolved.

Immune Checkpoint Inhibitors (ICIs)

Immune checkpoints are proteins on cell surfaces that prevent the immune system attacking cells indiscriminately. These play an important role in deactivating the immune response after a pathogen, such as a virus or bacteria, has been destroyed. Cancer cells have molecules (known as ligands) on their surface, which can bind with the checkpoint proteins on T-cells, effectively pushing the "stop" button on the immune system response.[34] Immune checkpoint inhibitors block this process, allowing T-cells to kill tumour cells by inducing apoptosis (programmed cell death). Examples of ICIs used in the UK are:

- **Ipilimumab** (Yervoy[35]) for advanced melanoma (skin cancer). It was approved by NICE (see page 4) for use in the NHS in 2012.[36]
- **Pembrolizumab** (Keytruda[37]) is offered on the NHS or through the Cancer Drugs Fund (see page 4) for a range of cancers and patient populations, sometimes in combination with ipilimumab or chemotherapy.[38,39,40]

Side effects of ICIs are linked to their overall boosting of the immune system. Common side effects (in around 10% of patients) can include pain and inflammation, fatigue, nausea, rashes and diarrhoea.[41] The treatment can also disrupt the functioning of the liver, kidneys and thyroid.

Radiotherapy

Radiotherapy technology in the UK has improved significantly over the past 20 years since becoming a priority for investment and development under NHS England's Cancer Strategy. There have been consistent advances in conventional external X-ray radiotherapy. The combination of new imaging and patient immobilisation techniques, and improvements in machine manoeuvrability, mean that radiotherapy is a highly precise and effective treatment. For example, intensity modulated radiotherapy uses lead "leaves" to shape the beam precisely to the tumour. Stereotactic ablative radiotherapy allows for radiation beams to be delivered from many different positions around the body.[42] The UK now has two Magnetic Resonance Linear Accelerator (MR Linac) machines in NHS hospitals, which use MRI scanners to account for organ movement during and between appointments.[43] The clinical role and value of these machines is an important clinical research question.

Proton Beam Therapy (PBT)

Proton beam therapy is a type of radiotherapy where a beam of high-energy protons is precisely targeted at a tumour, which is newly available in the UK (see Box 3). [44] Protons "drop off" faster than X-rays as they pass through the body, so PBT is thought to deliver less radiation to surrounding healthy tissue and vital organs. This is a particular advantage in children to reduce growth impairment, and when the tumour requires a high dose and lies close to a critical body part.[45] Clinical teams usually recommend PBT for children and patients under 25 years of age, or adults with treatment-resistant tumours close to the brain and spinal cord. However, the precision of the technique means that care has to be taken when treating tumours that are affected by organ movement or the patient breathing. This is the subject of intense research effort and national clinical trials.[46] PBT is therefore a promising new treatment, but there is still relatively little evidence of its superiority to X-ray radiotherapy in the long-term.

Box 3. New Proton Beam Therapy (PBT) Centres in the UK
New PBT centres at The Christie NHS Foundation Trust in Manchester and University College London Hospitals (UCLH) will provide a joint PBT service that meets the clinical need for the UK.[47] The NHS currently pays for UK patients to go abroad for PBT and it will now gradually transition to the new service. Having PBT available in the UK is more cost-effective and more convenient for patients. The Christie began treating patients in December 2018. UCLH's Proton Beam Therapy Centre will open in 2020. Between them, they will treat 1,500 patients per year. Both centres will track outcomes to monitor how successful the treatments are in the UK population and have facilities for world-class PBT research.[48]

Future areas for radiotherapy research include:

- **Combination with drugs.** Theoretically, PBT may provide even greater benefits than X-rays in combination with both conventional chemotherapy drugs and new immunotherapies.
- **Hypofractionation** refers to giving larger doses of radiotherapy over fewer treatment sessions (fractions) than is standard practice.[49] X-ray radiotherapy is

usually given at lower doses per fraction, five days a week, for multiple weeks. Research into delivering higher doses of radiotherapy has shown that hypofractionation can be performed effectively.[50,51] The potential benefits for patients are less toxicity, fewer hospital visits and improved tumour control. Trials will determine whether better results can be obtained using hypofractionation with protons.

Molecular Radiotherapy

Molecular radiotherapy involves attaching radioactive isotopes to another molecule or antibody, which carry it through the blood stream to the tumour site. In some cases the radioisotopes may be injected directly into the tumour. Radium-223 dichloride (Xofigo) is approved by NICE for use in the NHS for patients with prostate cancer that has metastasised to bone. A personalised approach to dosage (dosimetry), in which the patient is continuously monitored to assess tumour response to the radioisotopes, allows for more precise treatment.[52,53]

Selective internal radiotherapy is another molecular radiotherapy approach for patients with colorectal cancer that has metastasised to the liver.[54] Radioactive microspheres (glass or resin beads carrying yttrium-90) that are designed to lodge in small vessels around the metastases are injected into branches of the artery that supplies the liver. The microspheres emit radiation to kill the tumour cells and cut off the blood supply to the tumours.[55]

Oncolytic Virus Therapy

Oncolytic virus therapy uses naturally occurring or engineered viruses that selectively replicate in and kill cancer cells. Research is still at an early stage and has only shown effect in particular cancers. The most advanced virus therapy so far is talimogene laherparepvec (T-VEC), a modified herpes simplex virus. T-VEC is approved by NICE for some melanoma (skin cancer) patients.[56] The virus breaks open tumour cells, releasing antigens into the surrounding area, which induces an immune system response in the patient. In clinical trials, T-VEC appears to improve the effectiveness of immune checkpoint inhibitors.[57]

Combining Therapies

There is broad consensus that combining treatment technologies may improve on the efficacy of using single technologies. T-VEC is one example that is now recommended for use in combination with ICIs. ICIs are also commonly used in combination with chemotherapy drugs. Other research has found promising results from combining radiotherapy with immunotherapy.[58] The breakdown of cancer cells from radiation results in the release of tumour-associated antigens into the blood stream, which can boost the systemic immune response.[59]

Funding New NHS Cancer Treatments

The National Institute for Health and Care Excellence (NICE) appraises new treatments for use in the NHS and other health and care services in England, with equivalent organisations in the devolved nations. NICE makes recommendations on whether treatments should be used in the NHS and under what circumstances, based on clinical efficacy and cost-effectiveness. A drug is considered cost-effective if it falls within a set threshold–otherwise this money is considered better spent on other NHS services. NHS England and devolved administration equivalents will also assess affordability for their commissioning processes.

The Cancer Drugs Fund

The Cancer Drugs Fund (CDF) is a partnership between NHS England, NICE and pharmaceutical companies and funds promising new cancer drugs in England. The new approach to the CDF means that decisions about which drugs are funded is now part of the NICE appraisal process.[60] If a new cancer drug is considered promising in terms of clinical efficacy, but does not yet meet NICE's requirements, it can be recommended for funding through the CDF's Managed Access Agreement process for a pre-set period while more trial and real-world data are collected. This means that cancer drugs that have demonstrated clinical benefit in clinical trials can be accessed by NHS patients in a matter of months, rather than waiting for several years for longer term clinical trial outcomes to be collected. CAR T-cell therapy is a recent example of how this process can function to benefit patients–enabling access to a potentially curative treatment that may not have been considered cost-effective under previous funding and commissioning arrangements. Wales and Northern Ireland usually follow NICE decisions and have their own arrangements for funding treatments.[61,62] The Scottish Medicines Consortium approves drugs for use in NHS Scotland and does not have access to the CDF.[63]

Patient Access to Information

While the consensus among cancer experts is that there have been unprecedented advances in the field, most newer treatments are for specific patient groups. As treatment technology progresses, these approaches may be used for a wider range of cancers and patient groups if they are determined to be clinically effective, safe and cost effective. Patient access to research and lay summaries has improved public engagement with academic research. Social media provides new opportunities for community support for patients.[64] The move towards patient-centred care[65] means that patients can take a more active role in their treatment, and in decision-making processes such as the NICE appraisal committees[66] or the NHS England Involvement Hub.[67] However, clinicians have voiced concerns about the quality of information available online, which in some cases has led to an increase in demand for treatments that may not be clinically appropriate. Patients benefit from clear and accurate information about which treatments might work for them, and the risks as well as the potential of new technologies.[68] Oncologists and other health professionals can support decision-making about treatment options[69] using the best available evidence and good practice guidelines.

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