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CLINICAL PERSPECTIVES

Approved gene therapies in Australia: coming to a store near you

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Abstract

Gene therapy has been promising paradigm-shifting advances in medical science for over two decades. Broadly, it is defined as a human therapy in which an existing defective gene function is added to, replaced, edited or disrupted to achieve a clinical benefit, up to and including a potential lifelong cure. Although originally set out to treat monogenic disorders, gene therapy has since been utilised to treat neoplasia, cardiovascular and neurodegenerative diseases, as well as infections. The realisation of this therapy has been dependent on the achievement of fundamental milestones in medicine, from determining the human genome sequence to identifying effective vehicles for the gene of interest, ultimately facilitating gene delivery in humans. In this review, six approved gene and cell therapies available in Australia are described. Their efficacy, adverse effects, limitations and eligibility are discussed, as well as an overview of cost and future directions.

Introduction

In passing The Gene Technology Act in 2000,[1] Australia formally acknowledged the transition of this field from an experimental entity to a growing science with the potential to irrevocably change how our society viewed health, agriculture, national security and even self-determination. At that time, the Human Genome Project was ostensibly nearing completion, although in the ensuing years, the true complexity of gene expression and the role of epigenetics has become more apparent.[1] Since then, Australia has developed a robust framework within which genetically modified organisms are scrutinised and regulated. Innovation too, has occurred, and although clinical gene therapy is far from a panacea, several paradigm-shifting products have already been developed. Seven such treatments have been approved for clinical use in Australia.

In vivo gene therapies

Gene therapy can be categorised according to the site where genetic manipulation takes place, either *in vivo* or *ex vivo* (Fig. 1). Nucleic acid uptake in cells can be effected through a variety of physical methods, including electroporation and needle injection of naked DNA into the target tissue. Nusinersen (Spinraza), an antisense oligonucleotide delivered by intrathecal injection, modulates RNA splicing in neural cells, thereby re-establishing the function of the survival motor neuron gene

Abbreviations: AAV, adeno-associated virus; BCP-ALL, B cell precursor acute lymphoblastic leukaemia; CAR, chimeric antigen receptor; CRISPR, clustered regularly interspaced short palindromic repeat; CRS, cytokine release syndrome; DLBCL, diffuse large B cell lymphoma; DNA, deoxyribonucleic acid; EMA, European Medicines Agency; FDA, Food and Drug Administration; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICANS, immune effector cell-mediated neurotoxicity syndrome; IFNγ, interferon gamma; IL-6, interleukin 6; mAb, monoclonal antibodies; MHC, major histocompatibility complex; MLMT, multi-luminance mobility testing; MSAC, Medical Services Advisory Committee; RNA, ribonucleic acid; SMA, spinal muscular atrophy; TFL, transformed follicular lymphoma; TGA, Therapeutic Goods Administration; TMA, thrombotic microangiopathy; TNFα, tumour necrosis factor alpha

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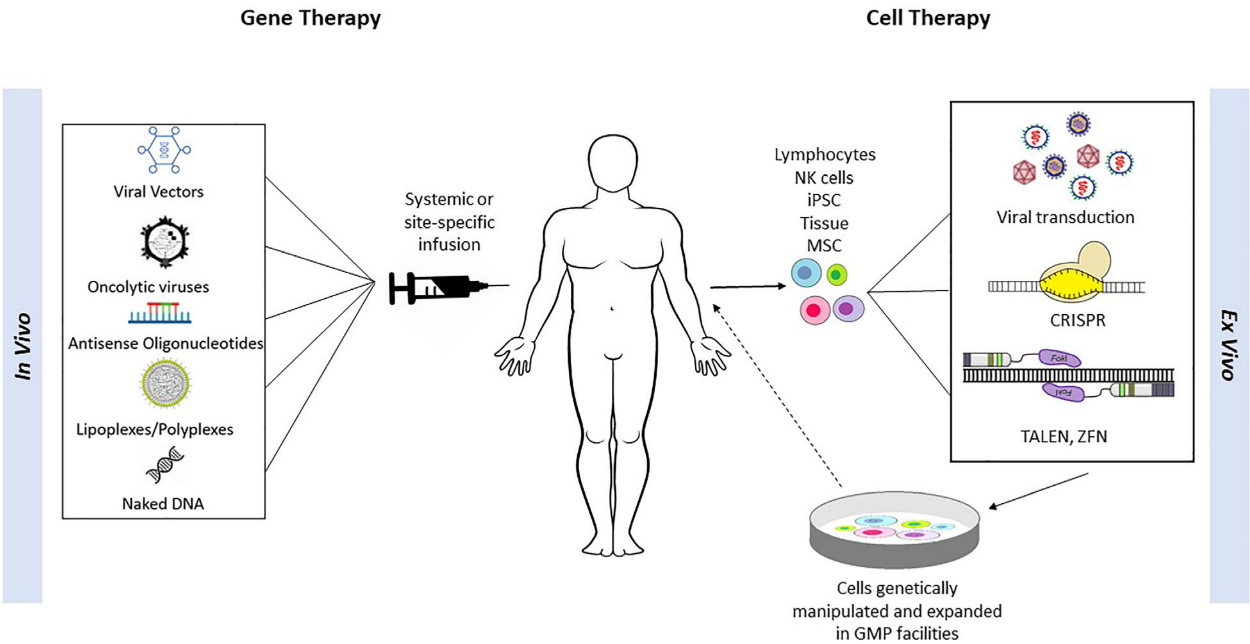

Figure 1 Classification and administration of gene and cell therapies. Molecular therapies are developed through either: *ex vivo* gene editing, where patient cells are harvested, genetically modified and reintroduced to the patient; or through *in vivo* gene transfer, where therapeutically manipulated nucleic acids are packaged and directly infused to take effect. CRISPR, clustered regularly interspaced short palindromic repeats; GMP, good manufacturing practice; iPSC, induced pluripotent stem cell; MSC, mesenchymal stem cell; NK, natural killer; TALEN, transcription activator-like effector nucleases; ZFN, zinc finger nucleases.

2 (*SMN2*). It was approved by the TGA for the treatment of spinal muscular atrophy (SMA) in 2017 and served as an important milestone in non-viral gene delivery (Table 1). Other non-viral vehicles such as lipoplexes and polyplexes, which are already commercially available as liposomal chemotherapies and antibiotics, have also been used experimentally for gene delivery. Oncolytic viruses can harness the natural ability of viruses to infect and kill cells, while having enhanced tumour recognition. Talimogene laherparepvec (Imlygic) is an attenuated herpes virus modified to express the granulocyte-macrophage colony-stimulating factor gene, which significantly reduced tumour size in inoperable melanoma following intratumoural injection. In 2015 it became the first approved gene therapy in Australia. Both Spinraza and Imlygic, although forerunners in their field, have since been overshadowed by the great leaps that have occurred in viral vector development. The most clinically successful viral delivery system is based on adeno-associated virus (AAV). AAV is the vehicle for the first three vector-mediated therapies approved by international regulatory authorities. Of these, Glybera, a therapy for lipoprotein lipase deficiency, was deemed commercially unviable and is no longer available. The other two therapies, Zolgensma and Luxturna, will be discussed herein (Table 1).

Mechanism of action

AAV, a member of the parvovirus family, is a small virus that is non-pathogenic in humans. It requires the presence of a helper virus (such as adenovirus) to replicate, but which rarely integrates into DNA, instead persisting in the nucleus as an episome. Furthermore, the different AAV serotypes have specificity for a broad range of tissues, making it an ideal vector in which to package smaller genetic payloads to specific organs.[2] In essence, the AAV genome is removed, with only two critical sequences remaining to flank the gene of interest. This vector is then introduced into cultured 'packaging' cells along with other structural and non-structural accessory genes, resulting in the production of recombinant AAV particles. The therapeutic gene then directs the expression of the deficient protein. In the decades since the first use of AAV in gene transfer experiments, considerable advances have been made in vector design and production to ensure efficient expression, and scaling these to allow high-volume production for clinical use.[3]

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Table 1 Summary of available gene therapies in Australia

Name (generic)	Product	Approximate cost (A$, '000s)	TGA Approval Year	Eligibility	Disease	Pivotal Clinical Trials (number of patients)	Outcomes
Imlygic (*Talimogene laherparepvec)*	Herpes oncolytic virus with *GM-CSF* gene	120	2015	Unresectable cutaneous, subcutaneous or nodal lesions after initial surgery	Malignant melanoma	OPTiM phase III randomised trial (436)[1]	ORR: 31.5% (vs 6.4) Median survival: 23.3 months (vs 18.9)
Spinraza (*Nusinersen*)	Antisense oligonucleotide	440 *per annum*	2017	5q homozygous deletion of *SMN1* or deletion of one copy of *SMN1* with a deleterious mutation on remaining copy in patients aged up to 18 years	SMA type I, II or IIIa	ENDEAR phase III randomised, double-blind, controlled trial (121)[2]	ORR: 73% OS at 1 year: 84%
Zolgensma *(Onasemnogene abeparvovec)*	AAV9 capsid with *SMN1* gene	2900	2021	Biallelic *SMN1* gene mutation, with 1–3 copies of *SMN2* gene, in patients aged up to 9 months	SMA1 SMA2	STRIVE phase III (22)[3] STRIVE-EU phase III (33)[4] STRONG phase I (32)[5]	ORR: 96% OS at 1 year: 95% Interim data shows signs of efficacy
Luxturna *(Voretigene neparvovec)*	AAV2 capsid with *hRPE65* gene	1200	2020	Biallelic *RPE65* gene mutation with sufficient viable retinal cells	Inherited retinal dystrophy	Phase III randomised control trial (31)[6]	ORR: 90%, 100-fold improvement in light sensitivity
Kymriah *(tisagenlecleucel)*	CD19/4-1BB CAR T cell	650 (BCP-ALL) 500 (DLBCL)	2018	Relapsed or refractory patients up to 25 years of age Relapsed or refractory after ≥2 lines of therapy, without primary CNS disease	BCP-ALL DLBCL	ELIANA phase II (75)[7] JULIET phase II (99)[8]	ORR: 81%, OS at 1 year: 76% ORR: 52% OS at 1 year: 48%
Yescarta (*Axicabtagene ciloleucel)*	CD19/CD28 CAR T cell	500	2020	Relapsed or refractory after ≥2 lines of therapy, without primary or uncontrolled CNS disease	DLBCL, PMBCL, HGBL, TFL	ZUMA-1 phase II (108)[9]	ORR: 82% OS at 1 year: 59%
Tecartus *(Brexucabtagene autoleucel)*	CD19/CD28 CAR T cell	520	2021	Relapsed or refractory after ≥2 lines of therapy, without primary or uncontrolled CNS disease	Mantle Cell Lymphoma	ZUMA-2 phase II (74)[10]	ORR: 92% OS at 15 months: 59%

BCP ALL, B cell precursor acute lymphoblastic lymphoma; CAR, chimeric antigen receptor; CNS, central nervous system; DLBCL, diffuse large B cell lymphoma; GVHD, graft versus host disease; HGBL, high-grade B cell lymphoma; ORR, overall response rate; OS, overall survival; PMBCL, primary mediastinal B cell lymphoma; SMA, spinal muscular atrophy; TFL, transformed follicular lymphoma.

Zolgensma (onasemnogene abeparvovec) for spinal muscular atrophy

SMA is a rare autosomal recessive condition arising from inactivating mutations in the gene encoding *SMN1*. Progressive degeneration of lower motor neurons results in muscle atrophy, ultimately requiring mechanical ventilation and assisted feeding. In SMA Type 1 (SMA1) and Type 2 (SMA2), death typically occurs in infancy or early adulthood. Zolgensma was formulated as an AAV9 vector and delivered as an intravenous infusion. After encouraging signals from early phase trials, two phase III trials involving 55 infants were conducted in centres around the world, including St Jude Children's Research Hospital and Great Ormond Street Hospital Biomedical Research Centre (Table 1). The clinical end-points of survival, motor function (as determined by a standardised scale), nutrition and respiratory function showed significantly improved outcomes compared with a historical cohort. In all, over 91% of patients survived to 14 months without permanent ventilation, compared with 26% within an untreated patient cohort, while 44% achieved independent sitting compared with no (0%) control patients.[4,5]

Early evidence from a phase I clinical trial has also demonstrated efficacy among patients with SMA2 after intrathecal injection[6] (Table 1). A phase I trial examining the effects of administration to pre-symptomatic, genetically confirmed cases of SMA1 showed significantly better motor outcomes compared to patients receiving treatment after onset of symptoms.[7] Based on these early data, Zolgensma was the second gene therapy to receive US Food and Drug Administration (FDA) approval for SMA1, SMA2 and preclinical SMA in 2017, with Australian TGA following suit in 2021.

Luxturna (voretigene neparvovec) for inherited retinopathies

Inherited retinal dystrophies are a group of disorders involving the gene encoding retinal pigment epithelium 65 kD (RPE65) protein. Although varying in age of onset and severity, most patients experience gradual degradation of photoreceptors, manifesting in night-blindness, with irrevocable progression to vision loss. Luxturna utilises an AAV2 vector encoding *RPE65* to treat children with biallelic mutations, who exhibit significant vision loss with adequate viable retinal cells. In a phase III randomised controlled trial conducted in two US sites, Children's Hospital of Philadelphia and University of Iowa, voretigene was administered as a subretinal injection to 21 patients (Table 1). The primary outcome measured changes in multi-luminance mobility testing (MLMT) scores, where participants navigated a course with various obstacles under diminishing light conditions.[8] Many subjective and objective secondary outcomes were also assessed. There was a significant improvement in MLMT, visual fields and light sensitivity at 12 months, with a trend towards improved visual acuity, all of which were sustained for 4 years after treatment.[9] Such marked improvements, in patients who would have otherwise progressed to blindness, led to FDA and European Medicines Agency (EMA) approval of Luxturna in 2017 and 2018 respectively, with TGA approval in 2020.

Adverse effects

Gene therapies carry certain risks, which to date have been generally theoretical, but still require diligent monitoring to detect their emergence. Foremost among these is the risk of genotoxicity, and the potential for oncogenesis resulting from off-target effects of the vector. Other side effects such as injury to the target organ by the vector, or more broadly the immune response elicited by the host after exposure, are equally vexing, as they may culminate in clearance of the virally transduced cells, rendering the treatment ineffective, and causing tissue damage in the process.

In the case of Zolgensma, excellent tolerability has been observed in clinical trials. Moreover, while the elevation of hepatic enzymes and thrombocytopenia were common (observed in 55% of participants) and attributable to the investigational product, all cases were transient, asymptomatic and responded readily to steroids.[4,5] All severe adverse effects (respiratory failure, pneumonia and dehydration) were related to the underlying condition. However, in the post-marketing phase, several important safety signals have emerged. Thrombotic microangiopathy (TMA), an immunological disorder of complement activation causing haemolysis, thrombocytopenia and kidney injury, was reported in four patients. Each instance of TMA resolved with treatment. Hepatotoxicity was observed in 90% of patients and in rare cases was associated with histopathological evidence of fibrosis. Even so, the elevation in serum aminotransferases was transient in all cases.

Similarly, Luxturna was extremely well tolerated in clinical trials, with only mild to moderate sequelae noted. These included ocular irritation, elevated intraocular pressure and maculopathy, the majority of which had resolved by 12 months.[8] After 4 years, apart from one case of retinal detachment, there were no drug-mediated side effects observed, and importantly, no immunological sequelae.[9]

Concerningly, recent evidence has emerged of neurological toxicity associated with Zolgensma and other

AAV-based therapies. Histological evidence of dorsal root ganglia inflammation was found in non-human primates after intrathecal injection, with a lymphocytic infiltrate throughout the spine and spinal nerves in varying degrees. Although no sensory neuropathy correlate has been found in human patients, it remains an area of close scrutiny.[10]

Patient experience

Long-term follow up and evaluation of patient-reported outcomes for approved AAV-based gene therapy are scarce at present. Moreover, obtaining accurate measurements of quality of life (QOL) data for SMA patients is complicated by the incapacitating nature of these diseases. Nevertheless, it is clear that improvement in functional status after treatment with Zolgensma is associated with marked improvement in QOL.[11] In the case of Luxturna, patient or parent-reported questionnaires demonstrated significant improvement in activities of daily living compared with baseline and control groups after 1 year.[12] This, in addition to the modest adverse effects, suggests a highly favourable patient experience for both therapies. Increasingly parallel control groups without crossover are difficult to achieve owing to the expectation of improvements by patients and their families.

Limitations

Various theoretical and actual limitations are associated with gene therapy, irrespective of the target disease. For AAV-based therapies, particularly those delivered systemically, the host–immune response can stymie clinical effects. A gene therapy trial for Duchenne muscular dystrophy (DMD; Solid Biosciences) was temporarily put on hold due to complement activation in two patients, thought to be triggered by a high viral load. Pre-existing antibodies directed against the virus surface can result in rapid clearance of the vector. T-cell-mediated destruction of transduced cells can limit therapeutic benefits.[1,2,13] Insertional mutagenesis, or the incorporation of exogenous genetic material into the host genome leading to deleterious mutations or aberrant gene activation, is a potential risk with grave consequences. Target-organ toxicity is one of the more serious safety signals that have emerged in some therapies utilising AAV. Most notable among these, four patients have died of liver failure and sepsis after receiving a high dose of an AAV8-based treatment for X-linked myotubular myopathy produced by Astellas Gene Therapies. This trial remains on hold. Such events, though rare, highlight the importance of strict regulation and long-term surveillance as gene therapy continues to develop. For clinicians, the process of obtaining consent when considering these therapies should include a discussion on these limitations.

Ex vivo cellular gene therapies

The second category of gene therapies is those where genetic modifications are made *ex vivo*. Typically, cells are retrieved, genetically modified and reintroduced to the patient (Fig. 1). The greatest clinical impact in this category has been achieved using cell-based immunotherapy, or cellular therapy. Immunotherapies harness the immune system's ability to fight infection and redirect it against the cells of interest. An early version of cell-based immunotherapy is allogeneic haemopoietic stem cell transplantation. First performed in 1957 to treat leukaemia, it is now a mainstream and highly effective cellular therapy for a variety of haematological and immunological conditions. Advances in the pharmacotherapeutic industry in the 1990s also resulted in the development of monoclonal antibodies (mAb), which could modulate the immune system through diverse mechanisms. mAb are more target-specific than conventional chemotherapy, but more importantly, have widespread uses beyond cancer. Since then, the field has undergone exponential growth, with development of more sophisticated direct therapies such as drug-antibody conjugates, and passive therapies that enhance the capabilities of the immune system, such as checkpoint inhibitors.[14] The potential for genetic engineering to further enhance immunotherapies has long been recognised. Combining immunotherapy and gene therapy was ultimately accomplished in the form of chimeric antigen receptor (CAR) T cells, which are now at the vanguard of personalised medicine.

Mechanisms of action

Tumour cells avoid immune-mediated destruction through a variety of mechanisms.[15] One important mechanism is their ability to evade detection by T cells by downregulating the expression of the major histocompatibility complex (MHC) Class I. This leads to their reduced recognition by cytotoxic T cells, and upregulation of inhibitory signals such as programmed cell death ligand PD-L1, which reduces T cell activation and proliferation.[16] By genetically programming T cells with CAR targeting a tumour-associated antigen irrespective of MHC expression (first-generation CAR) and incorporating enhanced costimulatory domains to induce lymphocyte expansion (second-generation CAR),[17] these diversionary tactics can be overcome in some cancers. The CAR T cells, once expanded *ex vivo*, can then be reintroduced into the patient where they target and kill cancer cells.

Tisagenlecleucel (tisa-cel) for B-cell malignancies

The second-generation autologous CAR T cell therapy tisagenlecleucel (tisa-cel, or Kymriah) was the first commercially available CAR T cell product, manufactured by Novartis in 2012.[18] Tisa-cel contains an extracellular CD19-specific single-chain variable fragment targeting B cells, with an intracellular 4-1BB costimulatory domain. In a clinical trial of paediatric and young adult patients with relapsed or refractory B cell precursor acute lymphoblastic leukaemia (BCP-ALL), tisa-cel demonstrated an excellent overall response rate of 81%, and 76% overall survival at 1 year[19] (Table 1). In 2017, tisa-cel was administered to patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL) and transformed follicular lymphoma (TFL) with similar encouraging results. The overall response rate was 52% and overall survival at 1 year was 48%[20] (Table 1). Further, CAR T therapy offered a considerable advantage over conventional salvage therapy, where relapsed or refractory patients only have a 2-year survival rate of 20%.[21] For a heavily pre-treated, adverse-risk group of patients, whose outcomes would otherwise be dismal, these results were pivotal. In 2017, tisa-cel received FDA approval as a treatment for both BCP-ALL and DLBCL, and the TGA approval for these indications in 2021 (Table 1).

Axicabtagene ciloleucel (axi-cel) and brexucabtagene autoleucel (brexu-cel) for B-cell malignancies

Axicabtagene ciloleucel (axi-cel, or Yescarta), first manufactured by Kite Pharma (since acquired by Gilead Sciences), was the second CD19-directed CAR T cell therapy to be tested in B cell lymphoid malignancies. In contrast to tisa-cel, it utilised CD28 instead of 4-1BB as its intracellular costimulatory domain. In 2015, 101 patients with DLBCL, TFL and primary mediastinal B cell lymphoma were enrolled in ZUMA-1, a phase II clinical trial. All patients were refractory to at least one line of therapy or experienced relapse within 12 months of receiving an autologous stem cell transplant. Treatment with axi-cel resulted in an overall response rate of 82%, with a complete response rate of 54%, and 1-year overall survival of 59%[22] (Table 1). Data from non-trial settings confirmed efficacy even in patients with poor prognostic features such as central nervous system involvement, lower performance status and previous allogeneic stem cell transplantation. Overall and complete response rates of 70% and 50% respectively were achieved, with a median duration of response of 11 months.[23] Based on these results, axi-cel was given FDA approval for the treatment of non-Hodgkin lymphoma and received TGA approval in 2020 (Table 1). Brexu-cel (or Tecartus), although identical in construction to axi-cel, utilised an additional manufacturing step, whereby CD19-positive tumour cells were removed to reduce the potential for *ex vivo* CAR T cell exhaustion. It was found to be effective in patients with relapsed or refractory mantle cell lymphoma[24] and received TGA approval for this in late 2021; however, it is not yet available or publicly funded in Australia.

Adverse effects

Adverse events related to CAR T cell therapies are primarily related to their immunogenic and myelosuppressive effects. Foremost among these is cytokine release syndrome (CRS), an excessive and sometimes life-threatening immune response characterised by overproduction of inflammatory cytokines in response to T cell proliferation and activity. Clinically, CRS is defined by fever, hypoxia and hypotension, and can present as mild flu-like symptoms or progress into a systemic inflammatory response with multi-organ failure. Tumour necrosis factor alpha (TNFα), interferon gamma (IFNγ), granulocyte-macrophage colony-stimulating factor (GM-CSF) and a host of interleukins are typically present. Interleukin 6 (IL-6) is particularly prominent, and direct suppression of this cytokine with the monoclonal antibody tocilizumab, as well as glucocorticoids, are routinely used in the treatment of moderate to severe CRS.[25]

Neurological toxicity is the second most common potentially serious side-effect in the acute period post-infusion. Immune effector cell-mediated neurotoxicity syndrome (ICANS) is associated with delirium, somnolence, language disturbance and tremor, with seizures, cerebral oedema and coma observed in severe cases. Hence, monitoring neurocognitive status is performed routinely in patients in the days and weeks following infusion. The underlying pathology, although not fully understood, is related to CRS. IL-6, IFNγ and TNFα directly activate endothelial cells, resulting in increased microvascular permeability, which renders the blood–brain barrier vulnerable to an inflammatory infiltrate.[26] Therefore, immunosuppression is also central to the treatment of ICANS.[25]

Patient experience

Patient-reported outcomes following CAR T cell therapy provide an important insight into the QOL of patients who respond to treatment. Several clinical trials have attempted to determine this using QOL questionnaires. In the ELIANA trial for BCP-ALL, all patients reported clinically meaningful improvement in physical, social and emotional functioning 28 days post-infusion compared with baseline. These functions continued to rise at 3-, 6- and 12-month time points.[27] Importantly, patient-reported outcomes were significantly lower in patients who did not respond to therapy, and there was considerable attrition at later time points due to patients being less likely to respond while unwell. These factors would lower the overall proportion of patients reaching a normative score (derived from a healthy population) of any parameter. Of those that responded, only 50% reported a normative score for physical condition at 1 year, indicating the sustained and possibly irreversible toll numerous lines of chemotherapy can take in this patient cohort.[27]

Limitations

Although the benefits of CAR T cells have endured, there are several limitations associated with their application. First, although the T cells are stimulated *ex vivo* for maximal expansion prior to infusion, they may diminish in number *in vivo* over time. A lack of persistence of T cells can occur due to inherent T cell senescence and exhaustion or terminal differentiation leading to reduced capacity for renewal.[28] The CAR vector can also play a role. CAR with higher affinity have reduced persistence and efficacy compared with lower affinity CAR,[29] and the CD28 costimulatory domain confers a lower lifespan than 4-1BB in CAR constructs. Last, CD19-negative relapse can also occur due to loss of antigen expression or immune pressure leading to lineage switch.[30]

Due to these factors affecting the longevity and efficacy of CAR T cells, some advocate consolidative allogeneic stem cell transplantation in eligible patients following remission. Practice in trials has been variable; however, there is clinical evidence that BCP-ALL patients who were transplanted after achieving complete remission with CAR T cells experienced a significantly longer progression-free and overall survival compared with those who were not.[31] Currently, no consensus guidelines exist on the role of transplantation following cellular therapy, and an individualised approach balancing the risk of relapse against the morbidity of a transplant is required. Thus, CAR T cell therapy still cannot be considered a panacea even for B-cell haematological malignancies.

Ethical considerations

The development and implementation of extremely costly treatments invariably raise concerns about the appropriate utilisation of limited health budgets, particularly where rare diseases are concerned. Is it justifiable to apportion vast sums to tertiary-level treatments when primary preventative strategies can have a far more durable and wide-reaching impact in health outcomes? Given that Aboriginal and Torres Strait Islander peoples have a life expectancy almost a decade below that of their non-indigenous counterparts, is a million dollars better invested in curing a single individual with retinal dystrophy or in health promotion in a remote First Nations community? Equally, such patients who progress to blindness require lifelong medical and disability support; the impact on carers as well as patients, from psychological, social, workforce and health perspectives, results in a very high financial burden to society. Taking this into account, the Medical Services Advisory Committee have concluded that the therapies outlined in this article are ultimately cost-effective; however, close ongoing scrutiny and review are essential where publicly funded therapies are concerned.

Additional concerns may arise from gene and cell therapies: the high resource input required to introduce such infrastructure,[32] the potential for environmental contamination, and as alluded to previously, the risk of genotoxicity may result in harm to patients. Last, while discussing the potential benefit to humans, the ecological cost of energy-intensive production methods is often overlooked. As we evolve into a global society where the carbon footprint of every action is dissected, the pharmacotherapeutic industry should be no exception.

Concluding: gene and cell therapies on the horizon

The future holds great promise for gene therapies. Clinical targets of CAR T cells may expand to include non-haematological malignancies and non-malignant conditions. Fourth-generation technologies utilising sophisticated gene-editing methods offer increased activity, longevity and off-the-shelf uniformity.[33] Trials have already demonstrated the efficacy of certain CAR T cell products as first- and second-line agents compared with conventional chemotherapy and may obviate the need for inferior salvage treatments.[34] AAV-based gene therapies for non-malignant indications such as haemophilia A[35] and B[36] are on the cusp of widespread approval. Early trials on CRISPR-Cas9-based *in vivo* gene editing have achieved success in a range of fields. Patients with transfusion-dependent β-thalassaemia and sickle cell disease had successful restoration of foetal haemoglobin synthesis after *BCL11A* downregulation, resulting in transfusion independence and freedom from vaso-occlusive crises,[37] while patients with hereditary transthyretin amyloidosis have experienced on average 87% reduction in transthyretin concentrations after CRISPR-Cas9-induced targeted DNA cleavage of the TTR gene.[38] Many small molecule gene therapies have also emerged in the wake of Nusinursen. Golodirsen is an antisense oligonucleotide that has been shown to induce significantly increased production of dystrophin in all patients by inducing exon skipping. In late 2019, based on successful clinical trials in Duchenne muscular dystrophy subjects, the FDA approved Golodirsen, which arose from research undertaken at the University of Western Australia. Two other small interfering RNA therapies are Patisiran and Givosiran for ATTR amyloidosis and acute hepatic porphyria respectively.[39] The burgeoning growth of the gene therapy industry is now a foregone conclusion and although this new era of therapeutics comes with some important caveats there is no doubt that they represent the heights of human ingenuity overcoming human frailty.

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