Cell and Gene Therapy: The Present and Future of Medicine

The 21st century has seen rapid advancements in the diagnosis and treatment of cancer and immune dysfunction diseases. The first step involves the diagnosis and risk stratification of solid organ cancers, haematological malignancies, and disorders of the immune system, which frequently require genetic testing. This genetic diagnosis paves the way for treatment of these disorders, which are fatal or associated with significant disability if left untreated. Recent progress in our knowledge of these genetic pathways has led to the creation of state-of-the-art treatments, such as CAR-T cells,[1] mesenchymal stem cells (MSCs),[2] and gene therapy.[3]

Cellular and gene therapies are potentially curative treatment options for a number of haematological and non-haematological disorders. The majority of these disorders have no other treatment options and are associated with high morbidity and mortality. There are only a few approved and growing uses for cell and gene therapy. These include acute leukaemia, large B-cell lymphoma, multiple myeloma, primary and secondary immunodeficiency, lung cancer, hepatocellular carcinoma, haemophilia, thalassemia, cystic fibrosis, and Duchenne muscular dystrophy. CAR-T cell and gene therapy offers a treatment with curative potential for these patients, who otherwise do not have any treatment options available.[4]

The world over, around 40–50% of patients with blood cancer treated with currently available treatments either fail to respond to initial therapy or relapse. Treatment options for these patients are limited, and the majority of them die of illness. Because cellular therapy has the potential to cure these patients, developing an in-house CAR-T therapeutic pipeline,[4] will provide a relatively cheaper option (Table-I). Although the research and clinical activity in this field has been predominantly carried out in the US, since 2014, Chinese academic institutions and commercial companies have endeavoured into CAR T-cell-based R&D. In June 2017, China surpassed the United States as the country with the most clinical trials in this field. To date, over 500 clinical trials are underway globally for CAR-T cell therapy, as well as more than 1000 clinical trials for mesenchymal stem cell therapy and gene therapy.[3]

Pakistan is the world's sixth-most populous country, with a high rate of consanguinity. In populations with high rates of consanguinity, genetic diseases are prevalent. In Pakistan, there is no cumulative data on the incidence of genetic diseases. However, according to a demographic survey, two-thirds of the marriages in Pakistan are consanguineous, which is one of the highest in the world. The Table-II shows the individual frequency of genetic disorders in the Pakistani population for whom gene therapy has received approval.[4]

Table-I: Diseases and Role of Centre of Cellular Therapy and Genomics

Diseases	Role of Centre of Cellular Therapy and Genomics
Diagnosis of inherited disorders of neurology, renal, immunodeficiency, hematological, malignant disorders	Next generation Sequencing testing
ALL	CAR-T cells
DLBCL	CAR-T cells
CLL	CAR-T cells
Follicular lymphoma	CAR-T cells
Multiple myeloma	CAR-T cells
AML	CAR-T cells
Duchenne muscular dystrophy	Gene therapy
SCID	Gene therapy
Hemophilia	Gene therapy
Hemoglobinopathy	Gene therapy
Cystic fibrosis	Gene therapy
Neurodegenerative disorders	Mesenchymal stem cell therapy
Autoimmune disorders	Mesenchymal stem cell therapy
Burns	Mesenchymal stem cell therapy
Osteoarthritis	Mesenchymal stem cell therapy
Infertility	Mesenchymal stem cell therapy
Dental scaffolds	Mesenchymal stem cell therapy
Cardiac remodeling	Mesenchymal stem cell therapy

CRISPR-Cas9 is a gene editing technology that is reproducible, relatively cheap, and has the ability to modify the genome by adding or removing DNA fragments. It has been successfully used to treat various malignant and non-malignant disorders that were previously considered incurable.[5]

In addition to CAR-T cell and gene therapy, another form of cellular therapy is mesenchymal stem cell (MSC) therapy, which is believed to repair and regenerate tissues affected by increasing age, immune dysfunction, hormonal abnormalities, and tissue damage. MSCs have recently gained attention for their adjunct use in moderate-to-severe COVID-19 cases. Prior to this, MSC therapy had already shown promise in the treatment of various immune dysfunction conditions like refractory systemic lupus erythematosus (SLE), Crohn's disease, systemic sclerosis (SS), rheumatoid arthritis (RA), multiple sclerosis (MS), graft versus host disease, diabetes mellitus, thyroiditis, and even different types of neurological disorders. At present, nearly a thousand clinical trials have used MSC-based therapies. MSCs have an inherent ability to homeostasize inflamed tissues. They have the potential to form cells like adipocytes, osteocytes, chondrocytes, hepatocytes, neurons, muscle cells, and epithelial cells, depending on the surrounding microenvironment. Multiple studies have also demonstrated that MSCs have intrinsic immunomodulatory and anti-inflammatory properties that can be used in the treatment of autoimmune and chronic inflammatory processes.

Table-II: Frequency of Genetic Disorders in Pakistan which are amenable to Treatment with Cell and Gene Therapy

Genetic Disorders	Frequency in Pakistan4
Beta thalassemia carriers	5-8%in general population 31% within families
Sickle cell disease	0.5 – 1%
Duchenne Muscular Dystrophy	0.5-1 / 10,000 male individuals
Cystic Fibrosis	NA
Hemophilia	~ 10000 cases of Hemophilia A & 2000 cases of Hemophilia B

Another evolving indication of cellular therapy is the use of cytotoxic T lymphocytes (CTLs) for the treatment of infectious diseases and autoimmune disorders. These CTLs can kill other cells directly and are seen as an important way to protect against a number of viral, bacterial, and protozoal infections, including HIV, measles, malaria, influenza, hepatitis B, and cytomegalovirus. They can also fight tumours. Autoimmune diseases happen when immune effector cells like cytotoxic T lymphocytes (CTLs), natural killer cells (NKs), macrophages, and immune effector molecules like complements, antibodies, cytokines, and others don't work right. These cells and molecules attack their own tissues or cells, which causes a pathological immune response and self-harm.

Ankylosing spondylitis, autoimmune encephalomyelitis (EAE), multiple sclerosis (MS), systemic lupus erythematosus (SLE), type 1 diabetes (T1D), rheumatoid arthritis (RA), graves disease, and vitiligo have all been treated with CTLs in a big way. The application of gene transfer-based strategies to use CTL in cancer cells is a recent key development. Several avenues of investigation are under development at this time.[6] CTL are likely to play a key role, justifying the widespread interest in targeting these key immune effector cells to treat cancer.

Cellular and gene therapy are the future of medicine. All major centers around the world are moving towards cellular and gene therapy as curative options for a large number of disorders for which no curative treatment exists. Not only blood cancers, but a large number of clinical trials for CAR-T cell and gene therapy are ongoing for solid tumours,[7] autoimmune disorders, neurological diseases, thalassemia, haemophilia, etc.

Granted, a significant portion of this work is still in the experimental phase, but the progress is so significant that it will take several years for these treatments to become standard of care. Therefore, in the near future, a growing number of patients with various malignant and non-malignant disorders will require and demand these treatments for their incurable conditions.

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