

Challenges in Global Access to CAR-T cells: an Asian Perspective

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Abstract

The use of cell therapy for clinical applications has seen a dramatic increase in recent years, primarily in oncology, especially with the use of chimeric antigen receptor (CAR) T-cell therapies. However, there are some barriers to the widespread adoption of CAR-T cell therapies globally, primarily because of the high cost of manufacturing these cells and clinical infrastructure considerations. We reviewed the different strategies adopted across Asia to implement CAR-T cell therapy and found that these included patient assistance programs, close engagement with funders, cost-effectiveness studies, on-site manufacturing of CAR-T cells, and joint ventures between local partners and foreign pharmaceutical companies. Although on-site manufacturing can reduce the cost of genetic engineering and expansion, it does not address many other hidden costs and quality considerations. Future growth in large-scale regional manufacturing, facilitated by cutting-edge science and innovation, could reduce costs through economies of scale and facilitate the eagerly needed global access.

Key words CAR-T cells, Asia, Global Access, Cell therapy

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Introduction

The global use of cell therapy has dramatically increased, particularly in cancer cell therapies. These include chimeric antigen receptor (CAR)-T cells, modified T cell receptors, natural killer (NK) cells, and other therapies, but most of the increase has been in the field of CAR-T cell therapy. For example, in 2022, an estimated 1,432 CAR-T therapies were administered, and this number appears to be increasing year-on-year^{1,2}.

Despite the success and utility of CAR-T cells, some barriers exist, including patient-centered factors such as the limited number of treatment centers and out-of-pocket costs such as travel, lodging, and meal expenses.

From the provider's perspective, there are logistics, staff time, resource constraints, and reimbursement uncertainties. There are also issues pertaining to the cost of manufacturing and difficulties in scaling up CAR-T manufacturing³.

An important limitation of CAR-T therapy is its affordability. To understand this issue, one must consider the differences in Gross Domestic Product (GDP) per capita among countries worldwide. CAR-T cells may be sold in the US for approximately US\$350,000 to US\$500,000, up to 6-8 times the GDP per capita for the US, which is approximately US\$66,100. However, for countries where the GDP per capita is significantly less, like China (US\$11,700) or India (US\$2,000), the cost

of CAR-T cells, as currently priced in the US, becomes 40 or even 200 times that of the GDP per capita⁴. If patients, governments, employer healthcare, or insurance schemes in these countries had to pay the same amount for CAR-T cells, many would not have been able to afford these therapies.

One way that is being explored to overcome this issue is through the use of on-site manufacture of CAR-T cells. This may reduce the costs of genetic engineering and expansion. However, there are still many challenges and other costs, including patient evaluation, selection, conditioning, and post-treatment recovery⁵. There are also many other hidden costs in setting up and maintaining a CAR-T cell manufacturing facility, including facility costs, hidden staffing costs, and release testing.

Availability and Funding of CAR-T Cell Therapy in Asia

Asia accounts for more than 60% of the world's population and 40% of its GDP⁶. The Asia-Pacific region has also accounted for 70% of global economic growth in the last two decades⁷. The adoption of CAR-T cell therapy is only at an early inflection point in Asia, with an estimated compound annual growth rate (CAGR) of 40%. Countries such as China, Japan, Korea, and Singapore have already conducted numerous CAR-T cell clinical trials, coupled with significant growth in commercial product usage, but many other Asian countries are still just beginning their CAR-T cell journey. However, countries with lower GDP per capita have difficulty accessing conventional commercial products; therefore, various strategies have been adopted to overcome this barrier. Through a survey of the coauthors of this paper, we compiled a snapshot of the current usage of CAR-T cells in Asia and the current approaches to facilitate the availability and funding of this important therapy.

China

Currently, two commercial CAR-T cell products in China are produced as joint ventures by global pharmaceutical companies, Kite and Juno⁸. Both target CD19 for B cell malignancies and are priced at approximately US\$175,000. Some commercial insurance systems pay approximately 50% of the cost. As of 2021, 342 clinical trials involving CAR-T cells have been conducted⁹. Most of these are investigator-initiated trials (IITs), which are funded by governments and donations. In contrast, a few are company-sponsored as part of investigational new drug (IND) applications (personal communication: He Huang).

India

India currently has no approved commercial CAR-T cell products. Indigenous CAR-T cell technology has been pioneered in India by the Indian Institute of Technology (Mumbai, India) in partnership with the Advanced Centre for Treatment, Research and Education in Cancer (Navi Mumbai, India)¹⁰. This investigational product has completed early clinical trials¹¹. The second investigational product being developed is by Immuneel Therapeutics, which has a CAR-T cell product in collaboration with and licensed from the Hospital Clinic de Barcelona and Institut d'Investigacions Biomediques August Pi i Sunyer¹². This investigational product has also completed phase 1 clinical trial¹³ and is currently in phase 2 trial¹⁴. In addition to these two programs, a collaboration has been established between Christian Medical College of India with Miltenyi Biotec to initiate a clinical evaluation of its product, though its potential licensing or commercial availability is unclear at this time¹⁵. Stempeutics Research is another major cell therapy company in India that has regulatory approval for the use of mesenchymal stromal cells for three clinical indications (<https://clinicaltrials.gov/show/NCT00883727>).

Indonesia

Indonesia does not have any commercial or clinical trials of CAR-T cell therapies (personal communication: Cosphiadi Irawan).

Iran

Iran has one "homemade" CAR-T cell clinical trial for pediatric patients where a local knowledge-based company manufactures the product¹⁶. This clinical trial is financed by the Council for Development Stem Cell Sciences and Technology of Iran (up to approximately 30%) and an investor (Amir Ali Hamidieh, the clinical trial's principal investigator).

Japan

Japan has a high-cost medical care reimbursement system supported by taxes, under which out-of-pocket medical expenses in excess of a certain amount (the co-payment limit) are reimbursed later. Commercial CAR-T cells in Japan include Kymriah, Yescarta, Breyanzi, Abecma, and Carvykti cells. All five drugs have the same price of 32,647,761 JPY, which is approximately US\$242,000. Most of the funding comes from public health insurance, and for most patients under 70 years of age, co-payments account for 30% of the total medical cost. A few ongoing clinical trials are supported by the Japan Agency for Medical Research and Development (AMED) and private funding (personal communication: Shin Kawamata and Satoshi Takahashi).

Korea

Korea has many approved cell therapies, most of which are in regenerative medicine. Currently, there is one commercial CAR-T cell product for cancer immunotherapy, Kymriah, which is priced at approximately US\$300,000. The National Health Insurance Service funds this, and patients pay only US\$5,000. There are more than seven CAR-T trials with a variety of targets, including CD19, BCMA, GPC2, and IL13Ra2 (personal communication: Bryan Choi).

Malaysia

Malaysia has a CAR-T cell product that is sold through Aux Therapeutics for approximately US \$40,000 to US\$50,000 (<https://www.auxtherapeutics.com/services>). Case-by-case approval is needed for access to this, and it seems to be funded by insurance; however, coverage varies according to the company. Government funding is also available for civil servants; however, approval is required. There is also an ongoing university trial with a private company for patients with diffuse large B-cell lymphoma (DLBCL) and acute lymphoblastic leukemia (ALL) (personal communication: Ng Soo Chin).

Singapore

Singapore has two commercial CAR-T cell products (Kymriah and Yescarta) that are sold at approximately US\$375,000. Patient assistance programs are available, and insurance programs partially cover the funding. Clinical trials for ALL, DLBCL, follicular lymphoma, multiple myeloma, and T cell lymphoma are ongoing. IITs are funded by philanthropy and grants, whereas IND registration studies are funded by companies (personal communication; William Hwang). Singapore has been working with neighboring countries to provide access to CAR-T cell therapy for patients with relapsed or refractory lymphoma using a unique hub-and-spoke model to optimize patient management of lymphoma in southeast and south Asia¹⁷.

Thailand

Two studies have been conducted. One was a collaboration between Chulalongkorn University and King Chulalongkorn Memorial Hospital and, the other, a collaboration between Mahidol University and Ramathibodi Hospital. Both were funded by the Thai government and philanthropic organizations (personal communication: Chaiyong Koaykul).

Potential Solutions to CAR-T Access Barriers

Various strategies have been proposed to address the barriers to CAR-T therapy. These include scaling up

CAR-T manufacturing, engaging community oncologists, expanding centers offering CAR-T treatment, and resolving financial issues such as CAR-T cell pricing, financial reimbursement, and out-of-pocket costs³. Spreading academic CAR-T cell manufacturing to every site and hospital does not necessarily solve these problems, as there are many hidden costs and issues related to variability in quality.

To address financial reimbursement, it is important to convince funding bodies to carefully analyze cost-effectiveness over a long period, as the effectiveness of CAR-T cells is best demonstrated by the sustained treatment-free remission seen in long-term survivors¹⁸⁻²¹.

Nevertheless, CAR-T cell prices remain high, and sharing costs between multiple payers is important to help in the payment of CAR-T cells. Governments can help patients with hospital subsidies, covering product costs, and grants. Insurance companies can assist with hospitalization, critical illness, and cell therapy product coverage. Pharmaceutical companies producing CAR-T cells can also help through patient assistance programs and subsidies, and philanthropy can provide support through programmatic funding and crowdfunding for specific patients.

Conclusion

In the long term, there should be a concerted effort to reduce the price of CAR-T cells by reducing the cost of equipment, reagents, vectors, and release testing. Innovations to reduce the time required to manufacture CAR-T cells and novel gene insertions can further reduce costs. The potential of allogeneic off-the-shelf CAR-T cells has been explored to allow for centralized manufacturing and achieve true economies of scale. However, further modifications and research are required, as they currently lack persistence²². Finally, consolidating manufacturing facilities can reduce costs by increasing the scale of manufacturing and reducing the impact of fixed costs. As more companies come on board for CAR-T cell manufacturing, controlled competition will reduce costs by allowing market forces to come into play.

Author Contributions

WH conceived and wrote the manuscript. All authors were involved in providing country-specific data as well as editing and approving the manuscript.

Conflicts of Interest

The authors declare no conflict of interest. Disclosure forms provided by the authors are available on the web-

site.

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