Developing academic cancer immunotherapy in Asia—lessons, challenges, and a vision for Thailand

Nattiya Hirankarn

Center of Excellence in Immunology and Immune Mediated Diseases, Department of Microbiology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Correspondence to: Nattiya Hirankarn, MD, PhD. Center of Excellence in Immunology and Immune Mediated Diseases, Department of Microbiology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand. Email: Nattiya.H@chula.ac.th.

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Cancer is the leading cause of death in Thailand, with approximately 70,000 deaths in 2014. This number has been increasing; therefore, representing a major health problem in Thailand. In Thailand, the 10 most common cancers in men are liver, lung, colon & rectum, prostate, lymphoma, oral, bladder, esophagus and stomach cancers. While the top 10 cancers in women are breast, cervix, liver, colon & rectum, lung, ovary, thyroid, lymphoma, uterus, and leukemia, respectively. Unlike in the West, hepatocellular carcinoma caused by chronic hepatitis B and cholangiocarcinoma pose a great health burden to the country, being the most common cancers, as a group, in men and the third most common among women. Another more common cancer in South East Asia including Thailand is Epstein-Barr virus (EBV)-associated nasopharyngeal carcinoma.

As a major medical breakthrough, immunotherapy has raised the hopes of cancer patients around the world. In particular, immune checkpoint inhibitors that lift off the brake from the tumor cells allowing T cells to work against and thereby attack the cancer cells, have led to successful treatment and survival outcomes for many late-stage cancer patients. For certain anti-cancer drugs with clear cost-effectiveness including imatinib for Philadelphia chromosome positive chronic myelocytic leukemia (CML-Ph+) and gastrointestinal stromal tumor (GIST) and trastuzumab for early stage HER2+ breast cancer are listed on the National List of Essential Medicines (NLEM) and can be reimbursed in Thailand. However, currently in Thailand most antibody-based targeted therapy and immune checkpoint inhibitors are available only to those patients who can be financially responsible for their own treatment. The cost of immune checkpoint inhibitor biologics is far too high for most cancer patients in developing countries. Thus, a main limitation for healthcare professionals has been accessibility to drugs that are already proven to improve long-term survival and quality of life in cancer patients.

There is a need for broader availability of these biologics at a more reasonable price. Several biosimilars for trastuzumab (Herceptin, the patent of which expired in Europe in July 2014) have been developed. However, the approval of these biosimilars remains a challenge. As a matter of national interest, as well as to secure a portion of the income generated in the biologics global market, it is important for Thailand to build local infrastructure and capabilities for the manufacture of biologics. This is a monumental task, considering the fact that there are limited biotechnology companies in Thailand. All pharmaceutical industries in the country only manufacture small molecule-based generic drugs with expired patents. There has never been any track record of developing a new original drug in Thailand. There have been several initiatives in the past 10 years to begin building the infrastructure and manpower needed for biologics development and production. The first life science company in Thailand, founded in 2009, is Siam Bioscience Co. Ltd., which is owned by Crown Property Bureau Equity Co. Ltd. in collaboration with Mahidol University. Siam Bioscience recently formed a joint venture with Cuba-based Center of Molecular Immunology (CIM) to develop biopharmaceuticals for cancer and autoimmune diseases. Biologics is also a focus

of the Thai authorities, predominantly the Ministry of Sciences and Technologies. A cGMP pilot plant was established in a collaboration between the National Science and Technology Development Agency (NSTDA) and King Mongkut's University of Technology Thonburi (KMUTT), as the first National Biopharmaceutical Facility (NBF). Regulations have been established for biosimilars by the Thai Food and Drug Administration (Thai FDA) to balance the quality and cost of production and for clinical trials. In fact, biologics guidelines that are in line with standards of the World Health Organization and Association of Southeast Asian Nations (ASEAN) were released by the Thai FDA in 2010. Currently, the Thai government has a mission, known as Thailand 4.0, to position the country as a life sciences hub. This policy includes the promotion of collaboration between government, private companies, and academic researchers. Besides budget from the government mainly to develop generic small molecule drugs and biosimilars for cancer, greater investment by the private sector in biotechnology is another key factor of in this mission. Recently, one of the largest public companies in Thailand, the Petroleum Authority of Thailand Public Company Limited (PTT), announced investment into the development of cancer drugs in a partnership with academic institutes. This is a tremendous development for the biopharmaceutical business and healthcare ecosystem in Thailand.

The regulation and production pipeline for biosimilars in Thailand has been established and Thai FDA has already approved few compounds including Infliximab biosimilar from Celltrion, Korea. Trastuzumab, Rituximab and Bevacizumab are under their review which expected to be approved soon. Thai FDA mainly follow the US FDA and EMA regulation. However, the policy of the current government is geared towards the abridged evaluation or assessment based on benchmark/reference agencies to speed up the process. The next phase is for Thailand to establish a therapeutic antibody center and other advanced pharmaceutical facilities to develop new biologic products. This is another necessary step toward true national medical security. The Chulalongkorn Center of Excellence in Systems Biology and Cancer Immunotherapy was recently established for research and development of antibody products.

In addition to immune checkpoint inhibitors, cellular immunotherapy using immune cells with or without genetically modified approaches, has been shown to be successful, which could change the course of treatment for patients with certain cancers. In 2017, use of CD19 CAR T cells was approved by the US FDA with striking success in refractory B cell leukemia and lymphoma. Other cell-based treatments have also been designated as orphan treatments by the European Union, including the use of NK cells in relapsed acute myeloid lymphoma and the use of EBV-specific T cells in EBV-associated cancers. The main limitation for these treatments is the lack of standard facilities and protocols, an obstacle that is also present in many countries throughout the world. All cellular or stem cell products that will be commercialized as part of diagnosis, therapy, or prevention in Thailand must be approved by the Thai FDA. Although the Thai FDA does not yet have a published guideline for advance therapy medicinal products (ATMPs), they have recognized the need to establish an official guideline that is mainly based on standards in the United States and Europe. Currently, a draft ATMP guideline produced by the Thai FDA is under consideration and awaiting the recommendations of experts in related academic fields before its official announcement. Similar to regulations for biologics and biosimilars, those for ATMPs in Thailand must be practical and should avoid overregulation, to balance the safety and cost.

Even as we can establish the infrastructure and protocols required for cell-based immunotherapy, the main limitation in Thailand is still the cost of treatment. The costs related to the patent issue as well as costs of the clinical-grade reagents needed to manufacture and expand cells to therapeutic doses remain too high for patients who have no additional public healthcare financial support. It is unlikely that countries with low GDP such as Thailand have health care policies that support very high-cost treatments. Even for hematopoietic stem cell transplantation, which is a standard treatment for various diseases, reimbursement from the Thai health care system is still limited. Future developments that can reduce the cost of treatment are needed. For example, the use of engineered T cells, such as CAR T cells or TCR-transduced T cells using nanoparticle-based delivery of DNA or RNA directly to target immune cells *in vivo*, will greatly reduce the enormous cost of cell expansion and regulation in the manufacturing process.

In conclusion, the hope for a cancer cure has come closer to reality with the exciting advances of cancer immunotherapy. It is imperative that academic institutions and healthcare centers around the world, including those in Thailand, must be prepared for this exciting field and to

gear up as much as possible to deliver on its promise.

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Footnote

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