Review Article

A review on paying for advanced cancer therapeutics: hard truths and realities in Asia

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Abstract: Health system expenditure on cancer drugs is rising rapidly in many countries given the high-priced novel treatments as well as the increasing usage due to a growing and ageing global population. The cost of cancer care continues to outstrip other diseases and it presents a global challenge to treatment access and cancer outcomes. Substantial variability exists in drug pricing across Asia, with low- or middle-income countries being heavily impacted. There is an urgent need to practice value-based pricing for oncology drugs. This will incentivize development of higher-value medicine and eliminate waste. Value-based assessments, financing infrastructure to assist appropriate prioritization, establishing domestic innovation and productive capabilities and reducing the unit economics of care are some of the measures that Asian countries should take towards ensuring universal health coverage for cancer care. Asia will need to keep driving cost management measures that are focused on drug pricing and simultaneously, should be encouraged to explore other interventions including centralising expertise for high "learning curve" efficiencies like chimeric antigen receptor (CAR)-T cell therapy. There is a call for more international collaboration within Asia and a continuous need to engage the public within each country, in order to ensure equitable access to effective cancer medications.

Keywords: Cancer drugs; immunotherapy; cost; financial infrastructure; value-based assessment

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Introduction

Asia is a continent of cultural diversity with 60% of the world's 7.1 billion people living here and it is estimated that the population will increase by another 1 billion by 2050 (1). With continued socioeconomic development and overall improvements in education, healthcare systems and standards, life expectancy across Asia has significantly increased. In 2016, approximately 12.4% in Asia was 60 years old or older, and is projected to increase to 1.3 billion people by 2050 (2).

An ageing population, changing lifestyles, increased urbanization and changes in diet, obesity, tobacco use and alcohol contribute towards the increasing cancer burden in Asian countries. In 2020, Asia accounted for 49.3% of the global cancer incidence (3). From 2008 to 2030, the incidence of cancer in Asia is estimated to be 74% (4), with cancer deaths projected to increase by 83% (5). There is a great diversity of socio-economic status in Asia, with

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1 country with a low income (LI) economy, 14 countries with low-middle (LM) economies, 9 countries with high middle (HM) economies and 14 countries with high income (HI) economies based on the World Bank Gross National Income (GNI) per-capita incomes levels (6). This diversity provides an opportunity to study the accessibility of cancer drugs and its impact on cancer costing.

The rise of immuno-oncology

The 1990s ushered in the era of molecular targeted therapy and more recently, the development of adoptive cell therapy with chimeric antigen receptor (CAR)-T cell therapy having a huge clinical impact on haematological cancers, often available only in HI countries. Bloomberg in collaboration with transparency market research (TMR) had recently projected the cancer immunotherapy global market to be valued at more than US $261.7 billion by 2031. There has been a continued rapid growth of immunotherapy drugs in preclinical and clinical development with a 22% increase from 2019 to 2020 (7).

Regional analysis from Bloomberg have also prognosticated that the cancer immunotherapy market in Asia Pacific will expand at rapid pace during this forecast period due to a rise in the number of clinical trials intended for and approved as new cancer treatments. A search in March 2023 on ClinicalTrials.gov with the key words "cancer", "immunotherapy" and "CAR-T" revealed a total of 138 clinical trials, to 41% (56 studies) come from East Asia.

As cancer is often seen as a debilitating disease and a threat to life, there is a strong desire to have the perceived best care, which tends to involve the latest cancer drugs. This drives up the demand, contributing to high cancer costs and is one of the limiting factors for access to these treatments. However, a recent study in China showed that anti-cancer drugs provided an only a marginal clinical benefit of 4.1 months in overall survival (8). China ranked the second-poorest affordability in a recent survey of six countries with a median monthly treatment price of $3,173 in 2016 for patented anticancer drugs (9). The cost of cancer care has outstripped other diseases and the high cost may not be associated with the clinical benefit nor the cost from research and development.

The cost challenge

Universal health coverage (10) should be the goal of all health care systems, to ensure that all people can receive essential cancer medications and high-value effective novel cancer treatments, without incurring undue financial cost. However due to the consequence of diverse economic development, healthcare policies and investments, Asian countries have vastly different healthcare priorities with every country's expenditure per capita on health care differing significantly (11). The European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) (12,13) incorporates a structured approach to clinical data interpretation to classify the magnitude of clinical benefit from anticancer therapies as well as its cost, promoting the accessibility and reducing iniquity of access to high value cancer treatments.

Given the wide differences in resources, clinical care practices, patient population, financial power, governmental healthcare structure and financing, inequity of cancer drugs availability exist within Asia. Access to cancer medications is limited when there is a high out-of-pocket (OOP) cost burden. In HM and HI countries, most of these medicines are on national coverage and available at a subsidised cost (14), however in LMICs and LICs, national drug coverage is limited and survey showed that in these countries, patients incur large amount of OOP, even for generic and inexpensive cancer drugs (14).

With the development of modern oncology, this has allowed the growth of precision medicine particularly in the field of targeted therapies, immune-oncology and gene and cell therapies. In turn, many pharmaceutical companies are working to develop "orphan" drugs in oncology and rare cancers which ultimately challenges traditional disease policies (15) and posing a significant burden for patients and health insurers (16). In Asia, pharmaceutical expenditure has seen an 6% per annum increased growth rate, with China, Thailand, Laos, Vietnam and the Philippines have increased expenditure on medications by 9% annually. Pharmaceutical spending is at an average of 31% of public sector expenditure on health care in Asia Pacific and it is clear that cancer medications form a large cut on this increasing cost (17).

On top of that, the prices of cancer drugs across Asian has a wide range (18). Due to the differences in economic supply and demand, comparisons have to be made based on purchasing power parity. A study across countries in South East Asia, Western Pacific and Mediterranean revealed that 26 cancer drugs corrected for form, pack size and doses had substantial differences in prices with ratios greater than 3 for 46% of drugs studied (19).

Patent laws are implemented internationally for cancer

drugs, with the aim to generate profits for pharmaceutical companies and originators to cover their costs during research and development, manufacturing, production, distribution and finally marketing. However, these costs are not transparent for all. A study that compared the sales income and the research and development costs for Food and Drug Administration (FDA)-approved cancer drugs from 1989 to 2017 showed that for the 99 medications in the analysis, the median income return at the end of 2017 was US $14.50 (range, $3.30–$55.10) for every dollar spent, even after adjustment for opportunity costs (20). High developmental and research costs have been used to justify the high prices of novel drugs however a justifiable price margin is still unclear. Lowering prices of cancer drugs and facilitating greater competition would be essential for improving patient access.

Governments in Asia has attempted to control costs in broadly 3 categories: (I) setting a ceiling price to innovation which government reimbursement is unable thus imposing downward pricing pressure, (II) establishing domestic innovation and production capabilities to increase competition, and (III) reducing the unit economics of care through examples of sharing of medications across patients, the use of biosimilars as well as compounding care.

China's healthcare reform

In 2009, China implemented a reform in her healthcare system ('2009 Reform'), with the aim to improve accessibility and affordability of her health-care services. The regulation of its drugs has been mainly drawn by four overlying systems: (I) quality supervision by National Medical Products Administration (NMPA), (II) bulk procurement by National Healthcare Security Administration (NHSA), (III) rational use management by National Health Commission (NHC) and (IV) insurance listing and pricing by NHSA (21).

China first introduced the zero mark-up policy and compensation reform in order to remove biased revenue incentives from prescribing and at the same time, establish a sustainable financing mechanism at the public healthcare (22). This policy was implemented across all their public hospitals by the end of 2017. NHSA now control drug prices using the form of reimbursement price, shifting from direct control on the retail price ceiling. In turn, the median monthly treatment price of domestic and imported drugs from the years of launch to 2022 had significantly decreased by 71% and 62%, respectively, with a recent study showing that the efficacy and safety of domestic anticancer drugs in China were comparable to that of imported drugs (23).

Setting a price ceiling in Asia

Value-based pricing is a strategy of determining prices of medication based on a patient or health system's perceived value of a product or service. In order to promote research and development while simultaneously contain the cost of drugs, Asian countries have used various strategies to settle the pricing of cancer drugs. These strategies include internal reference pricing, external reference pricing, special pricing agreements, pharmacoeconomic evaluations.

From 2017, China has been relying on evaluations and health technology assessments (HTA) in their implementation of national price negotiations for medications. Any drugs listed on the China's National Reimbursement Drug List (NRDL) are reimbursed at a national level, while a drug that has been approved by the NMPA but has not been listed on the NRDL are still available to patients but must be paid for privately.

In order to secure a place on the NRDL, pharmaceutical companies will need to significantly drop the prices of their drugs and this lower drug price negotiated may discourage pharmaceutical developments. However, in order to promote value-based anticancer pricing, there is a need for a more transparent and credible pricing approach. Zhang *et al.* (24) assessed the relation between negotiated price and value of anticancer medications on the NRDL since the implementation of price negotiations in 2017. His study included 75 indications of 46 branded anticancer medicines from 2017 to 2020 and found that the median daily costs for the anticancer therapies had reduced over the years, being priced at US $87.6, $71.8, $58.9, and $39.7, respectively. The authors concluded that while negotiation policy decreased prices of anticancer medications in China, however there was no statistically significant correlation observed between their costs and clinical benefits.

Healthcare in Singapore is financed based on the "S+3M" Framework consisting of: Medisave, MediShield Life and MediFund. Medisave is a compulsory, government-administered medical savings account that requires workers to contribute part of their wages in order to pay for major acute health care expenses. Medishield Life is a compulsory health insurance to pay for high-cost hospitalizations and selected costly outpatient treatment while MediFund is a means-tested social welfare programme meant for the

poorest Singapore citizens only.

Since 1st September 2022, Singapore implemented the Cancer Drug List: a list of clinically proven, evidence-based and cost-effective outpatient cancer drug treatments which can be claimed under MediShield Life. The agency for care effectiveness (ACE) is the national HTA agency established to demonstrate the impact and value of health technologies through scientific and economic assessments. The Cancer Drug List was developed using internationally standardised HTA methodologies to target funding to drugs that optimise health benefits within finite resources. The Singaporean government also set more granular claim limits to provide better coverage based on the cost of each treatment. Since these changes were announced, the Singapore Ministry of Health has been able to buy cancer drugs 30 per cent lower on average and in some cases, with prices dropping by over 60 per cents.

Establishing domestic innovation: "homegrown" immunotherapy

Competition in therapeutic products and selection of specialised centres with expert human resource to deliver such complex treatments may also drive down cost. The number of clinical trials testing drugs has rapidly increased in China, enhancing their research and development capabilities and the regulatory reforms. In February 2021, Novartis announced a collaborative licensing agreement with Bei Gene to develop, manufacture, and commercialize the company's anti-PD-1 antibody tislelizumab (25). Tislelizumab in combination with chemotherapy, was approved by the China NMPA for nine indications in China, among which has been approved for first line treatment of nasopharyngeal cancer, advanced squamous non-small cell lung cancer (26) and second line treatment for locally advanced or metastatic esophageal squamous cell carcinoma (27). Likewise, Innovent and Lilly's sintilimab (Tyvyt) (28,29) as well as Hengrui Pharma's camrelizumab (AiRuiKa) (30) has also been approved and made available for various indications by NMPA in China.

Since making it into the China's national reimbursement drug list, Sintilimab, as the first programmed death 1 (PD-1) inhibitor, was listed with a price reduction of 64% (31). A comparison of wholesale acquisition cost for the drugs showed significant discounts in China compared with U.S. cost. For example, nivolumab costs more than $16,000 every 4 weeks in the United States compared with about $7,000 every 4 weeks in China. For pembrolizumab, the comparison would be about $13,000 every 4 weeks compared with $8,000 every 4 weeks in China (32).

Despite these possible cost savings, United States FDA has rejected cancer drug submissions by pharmaceutical companies based on clinical trials that were mainly conducted in Asia (33), on the basis that they were concerned that these trials did not enrol a population diverse enough for the results to be applicable to patients in the United States.

China's CAR-T cell therapy

In 2017, Novartis's Kymriah (tisagenleuleucel) became the first CAR-T cell therapy in the world to achieve approval in the treatment of relapsed acute lymphoblastic leukaemia (ALL). Gilead Science's Yescarta (axicabtageneciloleucel) was subsequently approved for certain types of non-Hodgkin lymphoma (NHL).

While the early approvals were mainly in the Western countries, China has proven to be as productive as their Western counterparts. With an estimated population of 1.4 billion, China has the largest patient reservoir globally for clinical trials. As of 16th July 2023, 817 clinical studies on CAR-T cell therapy have been registered in China, with 604 trials on ClinicalTrials.gov and 213 trials on the Chinese Clinical Trial Registry. The high publication-to-trial ratio reflects the efforts that China has put into CAR-T cell research and clinical development. Both Novartis's Kymriah and Gilead Science's Yescarta passed NMPA inspection in June and July of 2021, respectively, and are now commercially available for patients with relapsed or refractory large B-cell lymphoma.

While more Asian countries move towards Universal Healthcare Coverage schemes that are targeted towards equity and affordability, traditional HTA may not be a 'one size fit all', particularly in evaluating new technology for therapeutics like CAR-T. Countries like South Korea and Japan have approved financial support for CAR-T therapy, though all were challenged to determine the appropriate funding pathway for reimbursement. Funding was achieved in 2019 for patients with paediatric acute lymphoblastic leukaemia (pALL) in Australia and subsequently in 2022 for adult patients with relapsed or refractory multiple myeloma in Japan. These approvals were made possible via a series of agreements which included local CAR-T innovators and the myriad of hospitals and patients' communities to allow for manufacturing and logistics of CAR-T to be done locally in order to bring down the cost of production.

Reducing the unit of economics of care: real world data (RWD)

The role of real world evidence and RWD beyond randomized controlled trials is important for early access and regulatory approval to reimbursement listing and commercialization. The safety and efficacy data obtained from clinical trials may not reflect the general Asian patient population and may have limited follow-up time. Within Asia, barriers identified included differences in definitions and terminology and non-standardised coding practices; the absence of longitudinal data; the absence of credible data processing and validation practices; and the inability to access and share RWD across different healthcare systems (34). In order to generate accessible and high quality RWD, there is a need to develop collaborative and synergistic research networks across multiple Asian stakeholders. In turn, this will have the potential to drive research to provide valid insights and reimbursements that policy-makers can adopt in order to improve healthcare delivery. In addition, there has been an increase in Asian representation across global clinical drug development, particularly for developed Asian countries, such as South Korea, China (Hong Kong), Malaysia, and Singapore. Through these clinical trials, patients are able to have early access to new drugs without waiting for regulatory approvals.

Patient access programs, vial sharing and biosimilars

In order to address the rising cost in cancer medication, many governments have come up with unique collaborations and innovative pricing strategies to cope. Patient access programs have been used to increase access to cancer drugs prior to regulatory approval, particularly in countries with high OOP payments or economically challenged populations. In Asia, this includes the Novartis CancerPath to Care program with eligible patients having access to ribociclib, letrozole as well as imatinib for breast cancer and gastrointestinal stromal malignancies (35) as well as the trastuzumab programs in the Philippines (36). Vial sharing and dose rounding have also shown, at a prescription level, to impact the costs of cancer drugs (37). Biosimilars are also another innovative method to decrease the cost of cancer medication expenditure within the countries of access as well, well studied in the example of Trastuzumab in human epidermal growth factor receptor 2 (HER2) positive breast cancer (38). Substituting branded cancer drugs to generics have also been shown to be an effective way to reduce cost.

Conclusions

Asian countries have a wide range of challenges that they will have to face against the tsunami of increasingly higher cancer drug costs that potential can impeded universal health care coverage, increasing the inequity of drug access and reimbursement. Large countries also suffer from urban-rural inequity including access to optimal care, discrepancies in public health implementation, timely screening and early detection, and with the "silver" tsunami of the ageing population in developed countries, these will only add to the challenge of balancing cancer costs.

This review aims to paint a brief summary on the landscape of cancer drug reimbursement however it remains limited as it will not be able to cover its entire complexity. Cancer drugs reimbursement and pricing policies will continue to change and develop over time and will grow beyond the scope of this article.

It is prime time for Asian oncologists, policy makers and healthcare leaders to collaborate through international efforts to readjust drug costs to allow for a balance between drug reimbursement and ideal access to critical cancer treatment. Strong public-private partnerships at national and regional levels are needed to prevent a 'perfect storm' of escalating cancer drug costs running further out of control.

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Footnote

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