

# ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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## Refining Dosing Strategies: Lessons From Singapore's Health Care System



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### **H&O** Could you provide an overview of the health care system in Singapore?

**BCG** The health care system in Singapore is centered on 2 basic tenets. First, the health care system attempts to make effective health care affordable and accessible to all Singaporeans. The second tenet is the principle of self-reliance and shared responsibility. I believe that the health care system has adhered to these 2 basic principles. The total health expenditure of Singapore is approximately 4.48% of the gross domestic product of the country. In absolute terms, this spending is substantial based on the per-capita gross domestic product. However, the government's expenditure on health care is approximately 30% to 35% of the total costs. (Currently, they are trying to increase this percentage of coverage to 40%.)

In terms of the worldwide health care indicators, including measures such as life expectancy, Singapore does well. Health statistics in 2020 showed that life expectancy in Singapore was among the highest worldwide, at approximately 86.1 years for women and 81.5 years for men. Overall, the health care system is efficient. It addresses the majority of the health care issues that arise in the population.

There are several caveats. It is still an evolution. Like other developed countries, the health care system in Singapore faces increasing challenges. Expenditures are rising. Advances in technology provide more options

for patients, but at greater expense. Medication costs are rising, and are likely to be unsustainable in the long term. There are various measures now in place to address these costs. The government in Singapore is currently promoting a strategy known as the "3 Beyonds." The "beyonds" are: beyond health care to health, beyond the hospital to community health services, and beyond quality to value. Quality can mean that all patients receive the best care, which is not sustainable in the long term.

### **H&O** How is health care financed in Singapore?

**BCG** Financing is centered on what we call the "3Ms." The first "M" is MediSave. Every Singaporean who is working has a mandatory proportion of his or her salary set aside in what is known as a Central Provident Fund. This fund consists of contributions from the employer and the employee. Approximately 5% to 10% of the fund is mandated for the worker's health care. The worker can use the money to pay for health care expenses as needed, but he or she cannot make direct withdrawals, and usage follows a rules-based co-payment model for medical bills incurred.

The second "M" refers to MediShield Life, which is a mandatory insurance plan that must be bought by every Singaporean. This insurance can be paid for with money from the worker's MediSave fund. MediShield Life covers the big bills. For example, if someone goes to a

hospital, the MediShield insurance will kick in to pay for large bills. MediShield also covers treatment for chronic conditions, such as chemotherapy, targeted therapy, and immunotherapy for patients with cancer. There are limits to its use. Currently, researchers are evaluating ways to restructure the MediShield Life insurance program. Previously, MediShield insurance allowed claims for approved treatments up to a ceiling, without considering the value of each treatment. Currently, the MediShield Life insurance program is being restructured to consider the value of treatment in the claim limits. MediShield Life insurance continues to cover retired people, who use their MediSave account to pay for the MediShield Life insurance premiums. MediSave can be drawn upon at any time during a person's life to pay for medical bills.

The third "M" refers to MediFund, which covers the small minority of people who do not work and cannot afford their remaining bills after exhausting other means of payments.

### H&O What are the advantages and disadvantages to the health care system in Singapore?

**BCG** There are several advantages. As a very small country, Singapore is able to tightly regulate the organization, delivery, and financing of health care. The health care system can be quite efficient in its adaptability and flexibility. It is possible to avoid excesses. The use of health care resources is scientifically grounded, and there are efforts to address future issues that may arise.

A disadvantage is that the system is highly complex. There are occasional adjustments that can impact the execution of patient care. Another disadvantage is that patients may not receive the most effective treatment, depending on their ability to afford it. This limitation is clearly explained to patients. The reason is that out-of-pocket costs are fairly high. These costs previously exceeded 40%, but now approximately 32% of the health care cost per person is out of pocket. This is still a substantial percentage, exceeding that in many other developed countries. However, it reflects the principle of responsibility for one's own health care. Implementation of the health care system in Singapore requires many regulations and policies, which may result in behavioral changes and practices that affect the utility of health care. For example, the government subsidizes acute hospital care, which is viewed as mandatory, as well as inpatient care. This coverage therefore discourages patients from being discharged. Patients tend to stay longer in the hospital because it costs more to stay in a step-down facility, such as a nursing home. These are some of the issues that we grapple with every day.

### H&O What is the drug approval process in Singapore?

**BCG** As with most developed countries, drug approval is centralized. In Singapore, drug approval is granted by a central authority called the Health Services Authority of Singapore under the Ministry of Health. If a pharmaceutical sponsor wants to register a new drug or product in Singapore before it is approved elsewhere, it must submit a full dossier. A full dossier is also needed if a company is submitting a new biosimilar or generic drug. The review of the dossier takes approximately 270 days, and the drug or product is either approved or not. The process is shorter if the drug or product has already received approval in a developed country, or from a so-called referenced authority such as the US Food and Drug Administration or the European Medicines Agency. An abridged version of the dossier must be submitted in these cases.

In Singapore, we generally adjust the dose according to the patient's body weight.

### H&O How are the dosages for drugs determined?

**BCG** The dosages are based on the available data submitted in the dossiers, and they also follow the FDA label. Physicians often make dose adjustments based on patient characteristics. Currently, there is a focus on implementing preemptive pharmacogenomics in clinical practice. With this approach, the drug dosages for each individual patient are adjusted as guided by best practice advisories incorporating pharmacogenomic evidence.

### H&O Can the dose of a drug be adjusted for certain patient populations?

**BCG** There is some evidence suggesting that ethnographic differences can impact the effect of drugs. There are several reasons why this could occur. For example, there may be pharmacologic reasons, such as differences in drug-metabolizing enzyme activity. It could be differences in the frequency of polymorphisms in drug-metabolizing enzymes. My colleagues and I performed a study showing that docetaxel as a treatment for lung cancer appeared

to be less tolerable in a predominately East Asian population in Singapore compared with a predominately Caucasian population in Sydney. Within Singapore, we have performed studies that examine this issue among the 3 major ethnic groups in the country: Chinese, Malays, and Indians (South Asians). South Asian patients tolerate docetaxel better than the Chinese or East Asian patients. Another example is 5-fluorouracil. Studies have shown that 5-fluorouracil is better tolerated in East Asian populations compared with Caucasian populations.

Another interesting point concerns drugs that are dosed according to body weight. Some expensive drugs are dosed this way. Pembrolizumab, an anti-programmed death 1 receptor (PD-1) monoclonal antibody, currently represents one of the top expenditures for drugs in Singapore. For non-small cell lung cancer (NSCLC), the label lists a flat dose of 200 mg every 3 weeks or 400 mg every 6 weeks. This dose was derived from a body weight formula of 2 mg/kg. The mean body weight of Singaporean Asians, especially cancer patients, can be approximately 50 kg. Therefore, a dose of 100 mg every 3 weeks—50% of the recommended dose—may be sufficient in this population. In Singapore, we generally adjust the dose according to the patient's body weight. By doing so, it is possible to save the patient money while achieving the same efficacy. My colleagues and I recently published a study analyzing real-world data for patients with NSCLC in Singapore. We showed that efficacy was similar with a dose of 100 mg or 200 mg. Our study provides validation for a dose-adjusted strategy.

Most oncology dose-response relationships are S-shaped. Some drugs are being dosed at the upper end of the S-shaped efficacy curve, where a reduced dose will not significantly affect efficacy. Furthermore, a decrease in the dose may reduce toxicity and thereby improve outcome.

### H&O How does the health care system in Singapore aim to optimize drug financing?

**BCG** In Singapore, we optimize drug prescribing to control costs. Our Ministry of Health has a financing body known as the Agency for Care Effectiveness. The purpose of this agency is to provide objective and credible health care guidance. Investigators at this agency perform health technology assessments and examine evidence, applying the latest methods of assessing value. They advise the Ministry of Health, which will then finance the drug according to the indication. There are deliberations to address the key decision of how much to subsidize a new drug compared with a standard agent. When discussing treatment options with patients, physicians will consider affordability in addition to efficacy. The patient occasionally must bear significant out-of-pocket costs.

### H&O Why is the health care system in Singapore amenable to the use of different dosing strategies?

**BCG** The key is that physicians have the flexibility to consider cost when discussing treatment options with the patient. For example, a very expensive drug, such as an anti-PD-1 antibody, may require a high co-pay that is not covered by any of the 3Ms (MediSave, MediShield, and MediFund). The patient will have to bear significant out-of-pocket costs. In this scenario, the physician will have the discretion to use a lower dose vs the full flat dose. The health care system allows this type of adjustment because it is not a fully reimbursed system. There is no third-party payer that will automatically reimburse the cost of the approved dose. Most patients will have to take cost into consideration. Affordability therefore comes into play.

A wider variety of vial sizes could also improve drug dosing.

### H&O Can any of the lessons learned from the health care system in Singapore be applied in the United States?

**BCG** One lesson is to start with a strong narrative that health care costs must be contained. In the long term, it is unsustainable to continue to pay for the best treatments and to continue to cover all of the public's health care requirements, even with third-party payers. Therefore, it might be better to start with this narrative and then tweak it along the way, allowing flexibility for deserving situations. This principle would compel physicians to consider the value of a drug, particularly from the patient's point of view. The value will vary according to the patient's circumstances. A patient may choose to receive or decline a treatment associated with a small amount of improvement.

In the United States, physicians are starting to consider value-based prescribing. They have all the indices available for each particular indication. Physicians know that a certain drug may have different efficacy in various clinical scenarios, and therefore the value will differ. These considerations help improve drug-prescribing habits.

A wider variety of vial sizes could also improve drug dosing. Continuing with the example of pembrolizumab, a single vial size of 200 mg does not provide much leeway

to change the dose. The availability of 100-mg vials might allow physicians to more easily dose the drug according to the patient's weight.

### H&O Do you have any other observations regarding the health care system in Singapore?

**BCG** The government has allowed the health care system to have flexibility. When the government can afford to do so, it provides subsidies to make out-of-pocket payments more manageable. For example, a few years ago, the government created the Pioneer Generation Package to subsidize health care costs for the approximately 450,000 Singaporeans who were born on or before December 31, 1949. The government recognized that these people helped build the country into what it is today. The government dedicated a considerable budget for this endeavor (although there is a cap per annum for each individual). The subsidies immediately decreased out-of-pocket payments for these citizens, most of whom are retired. The government was able to identify where the needs are. More recently, a similar program was established for a younger generation of people. This wise approach considers affordability from the government's point of view and provides subsidies according to where the needs are.

Another benefit to the health care system in Singapore is that it incorporates the goal of maintaining health—not just providing care—and also advocates the correct place to receive treatment. A full-care hospital, which is very expensive, might not be the right place. In addition, community health centers can provide good primary health care services and treatment for less complex conditions. Lastly, the system has made efforts to move from quality to value.

### Disclosure

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### Suggested Readings

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