

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Drug Development in the Pacific Rim

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H&O There has been an increased interest in drug development in the Pacific Rim in recent years. Could you explain the contributing factors behind this change?

JW Several factors have led to this. These include:

- An increase in the number of physicians trained in leading academic institutions who are returning to this part of the world—especially Singapore, Hong Kong, Taiwan, and Korea.
- Japan and Australia have had ongoing drug development programs for some time and are expanding to other regions in the area.
- The growth of Asian economies over the past 20–25 years has led to increases in education, expectations, economic power, and life span. Chronic disease has now become a major cause of morbidity and mortality. Currently, cancer is the leading cause of death in Singapore; and this has led to increased interest in the development of better therapy. A more educated population with greater earning capacity wants active, rather than symptomatic, treatment for cancer.

H&O What are the most prevalent types of cancer in Singapore?

JW There are some differences between the most common cancers in the United States and the Pacific Rim.

In Singapore, the most common cancers among men, in order, are lung, colorectal, hepatocellular, gastric, prostate, and nasopharyngeal. Among women in Singapore, the most common malignancy is breast, followed by colorectal, lung, ovary, and cervix.

H&O What are the specific needs pertaining to drug development in the Pacific Rim?

JW There are far more drugs available for malignancies that are more common in the West. The lack of treatment options for some of the common malignancies in the Asia-Pacific region is one of the motives for improving research and development in this part of the world. It is unreasonable to expect countries in which nasopharyngeal cancer, for example, is uncommon to invest in the development of better therapy for this disease.

In addition, certain cancers may express themselves differently among different populations. Drug response and toxicity as well can differ among different populations.

In the late 1980s, Dr. Mark Ratain and colleagues published a very interesting subset analysis of toxicity and efficacy data with amonafide, a drug that had been developed for the treatment of breast cancer. This analysis showed an increase in activity and toxicity among rapid acetylators. Most whites are slow acetylators and most Asians are rapid acetylators. It appeared that amonafide was acetylated to an active metabolite, which led to more activity as well as more toxicity. The drug was relatively ineffective in slow acetylators, but there was clear activity in rapid acetylators. Warfarin is another drug that shows significant variation in therapeutic dose due to different genetic patterns among ethnic groups.

These findings led me to question whether these differences might be true of other drugs. In Singapore, I noticed that doxorubicin and cyclophosphamide, common agents for adjuvant therapy in breast cancer, were associated with substantial toxicity among Chinese patients, whereas I found much less toxicity when using them among whites in North America. This difference had been recognized for some time, but it was thought to be due to a lack of training among the local physicians in correct administration of the drugs. However, as

I was privileged to do my residency and fellowship in the United States, the experience led me and my colleagues to believe that these differences warranted further evaluation. We presented a study at the 2002 Annual Meeting of the American Society of Clinical Oncology showing that standard doses of doxorubicin and cyclophosphamide in adjuvant breast cancer were more toxic among Asians compared to whites. Dr. Boon Cher Goh from our group has also published data showing that the area under the curve and clearance of docetaxel are markedly different between Asians and whites. So, not only do Asians and whites have differing rates of various cancers, there are also differences in the metabolism of certain drugs.

Another important issue specific to this part of the world is the prevalence of non-small cell lung cancer among Asian nonsmoking women, who have a much higher incidence of a mutation in the epidermal growth factor receptor (EGFR) that increases the response rate to small molecule tyrosine kinase inhibitors, compared to whites. Consequently, we see a much higher rate of response to small molecule tyrosine kinase inhibitors against EGFR, such as erlotinib (Tarceva, OSI/Genentech) and gefitinib (Iressa, AstraZeneca). If there were no drug development efforts in the Pacific Rim, gefitinib and erlotinib may not have been developed, because the response rate among white populations is low.

H&O How might Western countries benefit from increased drug development in the Pacific Rim?

JW There are many potential benefits. As an example, hepatocellular cancer is common here, although the rate is declining mainly because the majority of cases are due to hepatitis B, for which there is a successful vaccination program in place. In North America and Western Europe, a common cause of hepatocellular carcinoma is hepatitis C, for which there is currently no vaccine. We may be able to develop therapeutic strategies for hepatocellular carcinoma in Asia that will benefit North America and Western Europe, where the rate of this disease is predicted to surge due to the increased rate of hepatitis C infection.

H&O Do you envision drug development becoming more of a global effort in years to come?

JW Yes, I think that drug development should be done on a global basis. Drug development is currently focused in regions where there is a market share. Because the market share in Asia has been so low, there has been little interest in conducting drug development in this region. However, the realization that there are differences between Asians and whites in terms of response and toxicity has piqued

industry interest. At the same time, Asian economies are rapidly growing, life expectancy is increasing, and the population is aging. It has been predicted that over the next 20 years, the world's cancer burden will shift geographically, with Asia comprising more than half the worldwide cancer population.

H&O In general, do countries in the Pacific Rim have the infrastructure necessary to handle the high cost of treatment?

JW It depends on what is meant by infrastructure. Many governments in the region do not subsidize many of the new agents, especially the molecularly targeted agents. Many drugs, such as the taxanes and the biologic agents, are unaffordable to a large proportion of the population.

Academic institutions in the newly developed Asian countries have thus invested heavily in developing the infrastructure to conduct drug development at international standards. Drug trials could be completed at a lower cost in Singapore, for instance, than in the United States. As an example, a computed tomography scan of the chest, abdomen, and pelvis costs approximately US\$500 in Singapore, substantially less than what this procedure costs in North America. Further, conducting clinical trials on a global basis means that patients can be accrued faster, possibly shortening the number of years required to develop a drug. It may be possible to work with groups that can better determine the go/no-go decision earlier on. Ultimately, the cost and time required could be reduced.

H&O How is the concern about proper training being addressed?

JW Singapore and other newly developed countries in the region have sent staff to leading US, UK, or Australian centers for significant training periods. We have also been fortunate that some of our citizens have returned from these countries after completing a full residency and fellowship. Our goal is to convince regulatory and government agencies and pharmaceutical companies that the local institutional review boards (in the Cancer Therapeutics Research Group [CTRG] described below, our institutional review boards are registered with the Office of Human Rights Protection of the United States) operate at international standards and that the doctors, nurses, and pharmacists at our institutions are trained to international standards. Patient safety and their rights are of paramount concern and must never be jeopardized. If we keep this in mind and at the same time aid companies in accelerating the drug pipeline and reducing cost, I believe we will have made a significant global contribution to drug development.

H&O Are there local biotechnology companies?

JW Two small biotechnology companies recently started in Singapore: Merlion, which specializes in natural products, and S*Bio, which focuses on small molecules and other synthetic compounds. Both companies are run and advised by people with extensive experience in drug development. At S*Bio, the scientific advisory board is chaired by Dr. Simon Campbell, Fellow of the Royal Society and Editor-in-Chief for the journal *Current Opinion in Drug Discovery and Development*. Prior to his retirement in 1998, he was the Senior Vice President for Worldwide Discovery and Medicinal R&D for Pfizer in Europe. Members of the board include Dr. Randall K. Johnson, former Director of Oncology Research at SmithKline Beecham and GlaxoSmithKline, Dr. Edison Tak-Bun Liu, Professor of Medicine at the National University of Singapore and Executive Director of the Genome Institute of Singapore, formerly Director of the Division of Clinical Sciences at the National Cancer Institute (USA), Dr. Elizabeth Eisenhauer, Professor in the Department of Oncology at Queen's University, Director of the Investigational New Drug Programme of the National Cancer Institute of Canada (NCIC) Clinical Trials Group and currently Vice-President of the NCIC, and myself.

H&O Is there a local clinical trials cooperative group?

JW Yes. Several years ago James Bishop of Australia and I formed the CTRG, which is currently the only international multicenter adult medical oncology cooperative academic group in the Asia-Pacific region. This group specializes in phase I and early phase II trials. It is based at the National University of Singapore and the National University Hospital, and has as its members the National Cancer Center of Singapore, Johns Hopkins International Medical Center, Singapore, the Sydney Cancer Center,

University of Sydney, the Sir Charles Gardiner Hospital, University of Western Australia, the Chinese University of Hong Kong, and Yonsei Cancer Center, Yonsei University, South Korea.

This group has the unique opportunity to conduct prospective clinical trials in both Asian and white populations, with tumor spectrums that cover the most common cancers affecting most of the world.

The group holds monthly teleconferences, meets four times per year, and has its own audit committee which audits each institution on a regular basis. The group conducts clinical trials for pharmaceutical companies and for government organizations such as the National Cancer Institute, both directly, and as a subcontractor of the phase II consortium run by the Mayo Clinic for the National Cancer Institute. The group's Web site can be accessed at www.ctr.org.

Suggested Reading

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