Anticancer Drug Discovery and Development Throughout the World

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Abstract: **This year's American Society of Clinical Oncology International Symposium devoted 2 hours to a lively discussion of various aspects of anticancer drug discovery and development throughout the world. The scientific program started with an overview of efforts directed toward promoting international collaboration in natural product–derived anticancer drug discovery. This was followed by a discussion on the importance of interethnic differences and pharmacogenetics in anticancer drug development. Thereafter, this part of the program was completed by a description of the activities of the newly created Singapore-Hong Kong-Australia Drug Development Consortium and an overview of the contribution of Japan to anticancer drug development. The logistics and regulatory aspects of clinical trials with new anticancer agents in different parts of the world were then presented, with an emphasis on Europe, North America, and Japan. The program was completed with a panel discussion of the efforts to harmonize the exchange of clinical data originating from one region of the globe with other territories, with input from official representatives of the United States Food and Drug Administration and the Medical Devices Evaluation Center of Japan.**

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IN THE YEAR 2000, approximately 10 million new cases of cancer were diagnosed, and there were 6 million cancer-related deaths. Taken together, 22 million people were living with cancer that had been diagnosed within the previous 5 years. These figures reflect a 22% increase in cancer incidence and mortality in the world in comparison with the year 1990. The most prevalent types of cancer in the year 2000 were breast (17.2%), colorectal (10.6%), and prostate (6.9%). The tumor types with the highest worldwide incidence were lung (12.3%), breast (10.4%), and colorectal (9.4%) tumors (Fig 1).[1]

There were approximately 5.3 million new cases of cancer in men, with 4.7 million cancer-related deaths. The tumor types with the highest incidence in men were lung, stomach, prostate, colorectal, and liver tumors. The highest mortality was due to cancer of the lung, stomach, liver, colon/rectum, and esophagus. In women, there were 4.7 million new cases of cancer, with approximately 2.7 million deaths. The tumor types with the highest incidence in women were breast, uterine cervix, colorectal, lung, and stomach tumors, with the highest mortality rates from cancer of the breast, lung, stomach, colon/rectum, and uterine cervix (Fig 2).[2]

THE PROBLEM OF CANCER IN DIFFERENT GEOGRAPHIC REGIONS

In the year 2000, the world population was approximately 6 billion people, with a projected increment of approximately 80 million new individuals per year. Based on these figures, the world population will reach 7.5 and 8.9 billion

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M.J.R. is a coinventor on two issued patents related to irinotecan and has significant financial relationships with several companies that have a major interest in topics mentioned in this article. These companies include Variagenics, a pharmacogenomics company focused on oncology (chair of Scientific Advisory Board), Xanthus Life Sciences, a company developing amonafide (consultant), and Datatrak International, a company providing global electronic data capture services (director).

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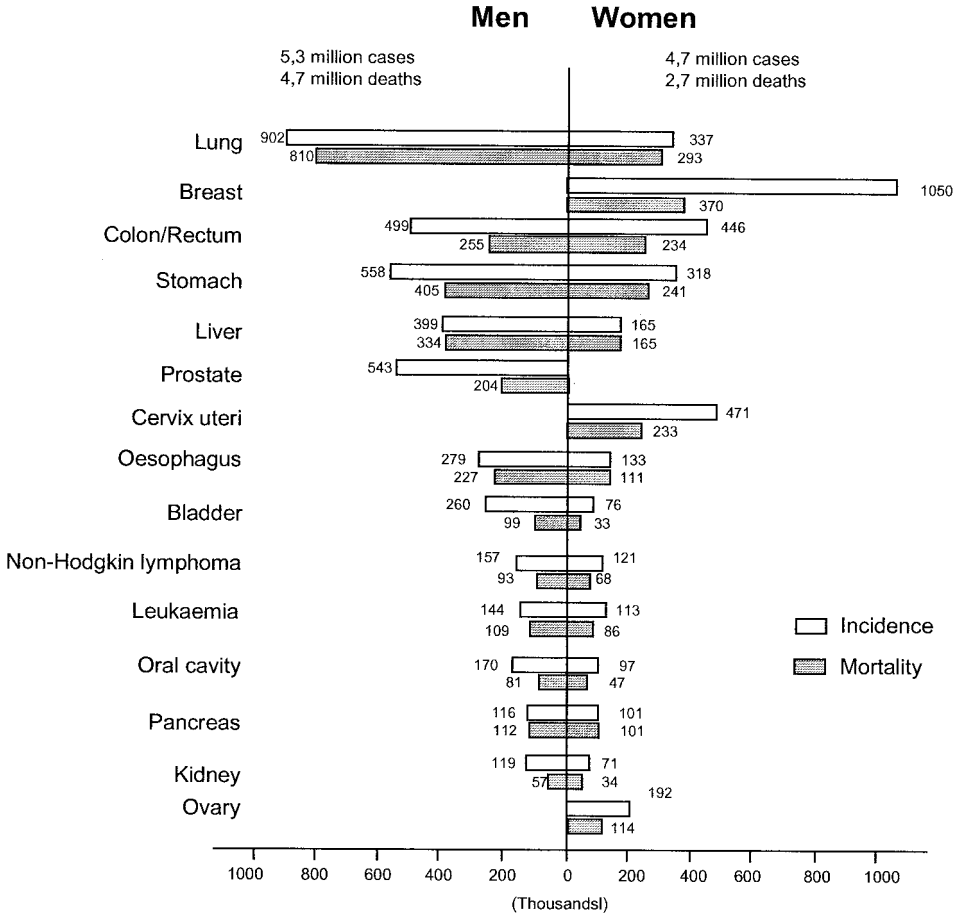

Fig 1. Estimated numbers of new cases (incidence) and deaths (mortality), by sex and site.

inhabitants in the years 2020 and 2050, respectively. This population growth rate, however, will not occur uniformly in the various geographic regions of the world. The growth rate will be more pronounced in developing countries and may be even negative in some developed countries (Fig 3).[3]

As a result, the population will peak in developed countries around the year 2020 and tend to decline thereafter; it is estimated to be approximately 2% below the year 2000 figure in the year 2050. The population living in North America and Europe will decrease from 17% to 11.5% during the same period of time. In contrast, an increase of approximately 63% will be observed in the population from the year 2000 to the year 2050. This expansion will be more pronounced in Africa, where the population will be double in the year 2030 (Table 1).[4]

The significant increase in the life expectancy of the population was an important characteristic of the last century. In developing countries, life expectancy rose from approximately 41 years in 1950 to 64 years in the year 2000. For these countries, it is expected to reach 71 years in the year 2020. Consequently, the proportion of individuals above 65 years in developing countries will increase from 14% in the year 2000 to 25% in the year 2050.[3,5,6]

This marked growth in the world population that should be accompanied by a significant increase in the life expectancy of the population will have direct consequences on the cancer incidence in the world. The total number of new cases of cancer will rise from 10 million in year 2000 by approximately 25% in each decade, reaching 24 million new cases per year in the year 2050. The total number of deaths will rise from 6 million in the year 2000 to 10 million in 2020 to over 16 million in the year 2050.[4,7]

In the year 2050, there will be 17 million new cases of cancer in less developed countries, while only 7 million new cases of cancer will occur in the more developed countries. Therefore, public health authorities should expect cancer to become a major challenge not only in developed countries but (especially) in developing countries as well.[2,7,8]

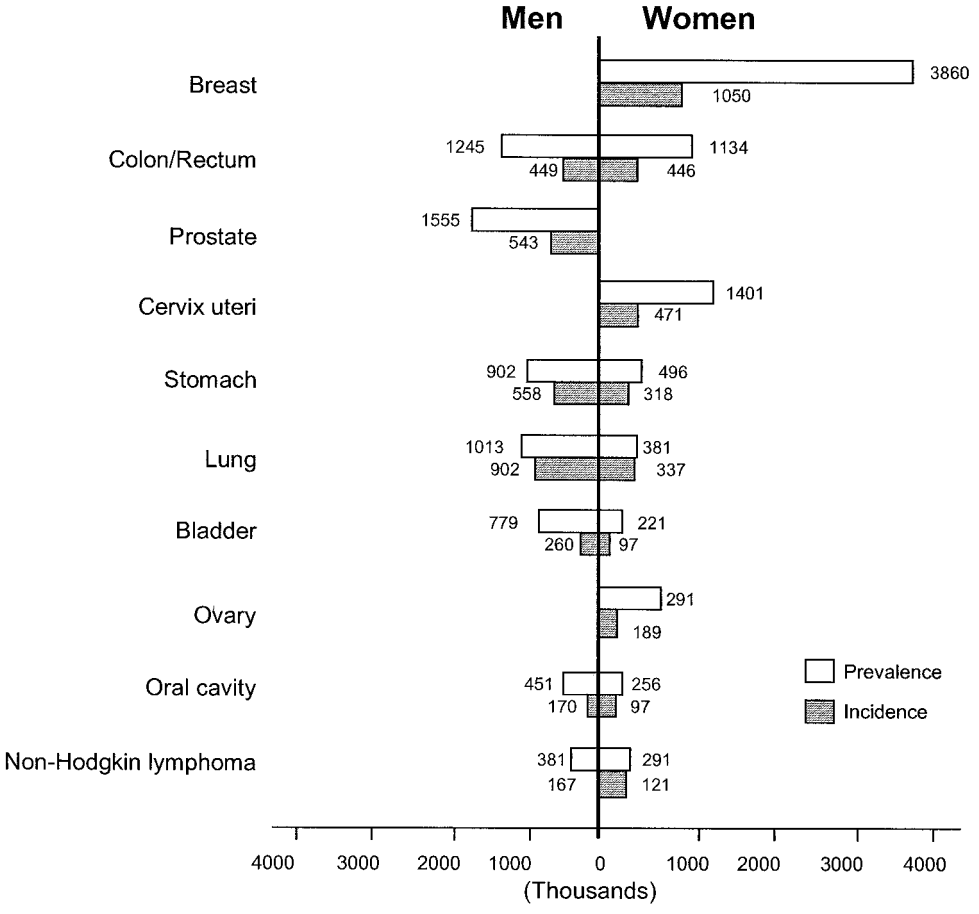

Fig 2. Estimated numbers of new cases (incidence) and prevalent cases (alive within 5 years of diagnosis), by sex and site.

EFFORTS IN NATURAL PRODUCT–DERIVED ANTICANCER DRUG DISCOVERY

Terrestrial Sources

Plants have a long history of use in the treatment of cancer, though many of the claims for the efficacy of such treatment should be viewed with some skepticism because cancer, as a specific disease entity, is likely to be poorly defined in terms of folklore and traditional medicine.[9,10] Some plant anticancer drugs in clinical use or development are listed in Tables 2 and 3.

Micro-organisms are a prolific source of structurally diverse bioactive metabolites and have yielded some of the most important products of the pharmaceutical industry. These include antibacterial agents, such as the penicillins (from *Penicillium* species), cephalosporins (from *Cephalosporium acremonium*), aminoglycosides, tetracyclines, and other polyketides of many structural types (from the *Actinomycetales*); immunosuppressive agents, such as the cyclosporins (from *Trichoderma* and *Tolypocladium* species) and rapamycin (from *Streptomyces* species); cholesterol-lowering agents, such as mevastatin (compactin; from *Penicillium* species) and lovastatin (from *Aspergillus* species); and anthelmintics and antiparasitic drugs, such as the ivermectins (from *Streptomyces* species). Antitumor antibiotics are among the most important of the cancer chemotherapeutic agents.[11] Some clinically useful drugs and agents in development are listed in Table 4.

Marine Sources

The world's oceans, covering more than 70% of the earth's surface, represent an enormous resource for the discovery of potential chemotherapeutic agents. Of the 33 animal phyla listed by Margulis and Schwartz,[12] 32 are represented in aquatic environments, with 15 being exclusively marine and 17 being both marine and nonmarine (with five of these having $> 95\%$ of their species only in marine environments), and only one, *Onychophora*, is exclusively nonmarine (Table 5).[13,14]

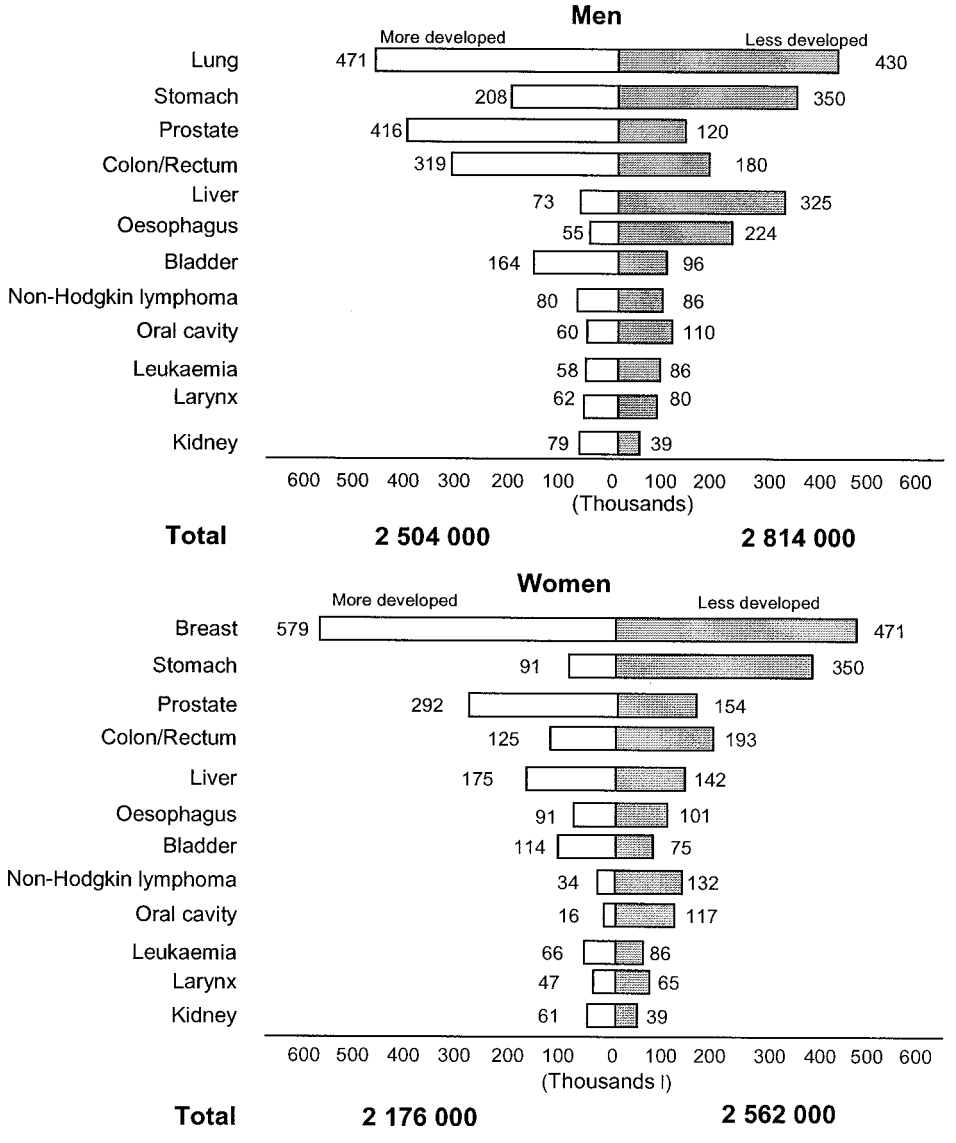

Fig 3. Estimated numbers of new cases in more developed and less developed countries. The 12 most common cancers in each sex are shown.

Before the development of reliable scuba-diving techniques some 40 years ago, the collection of marine organisms was limited to those obtainable by skin diving. Subsequently, depths from approximately 10 feet to 120 feet became routinely attainable, and the marine environment has been increasingly explored as a source of novel bioactive agents. The marine environment has proved to be a prolific source of structurally novel bioactive agents, and several have advanced to clinical development as potential anticancer agents.[10,11,15]

The interest in nature as a source of potential chemotherapeutic agents continues. An analysis of the number and sources of anticancer and anti-infective agents, reported mainly in the annual reports of *Medicinal Chemistry* from 1984 to 1995 covering the years 1983 to 1994, indicates that more than 60% of the approved drugs developed in these disease areas can trace their lineage back to a natural product structure.[9,11]

National Cancer Institute's Drug Discovery Strategy

From the data in Tables 2 through 4, it is clear that drugs representing a wide range of molecular diversity are derived from diverse natural sources found in many regions worldwide. The National Cancer Institute (NCI) in the United States has been exploring nature as a source of potential new anticancer drugs since 1955, and continues to collaborate with many countries in this endeavor.[9]

Table 1. Estimated and Projected Numbers of Cancer Cases

Region	Years			
	2000	2010	2022	2050
World	10.06	12.34	15.35	23.83
More developed regions	4.68	5.31	6.03	6.79
Less developed regions	5.38	7.03	9.32	17.04
Africa	0.3	0.79	1.04	2.53
Asia (Japan)	0.52	0.61	0.67	0.65
Asia (other)	3.94	5.17	6.75	10.74
Europe	2.77	3.06	3.36	3.64
South America	0.83	1.10	1.48	2.88
North America	1.38	1.65	2.03	2.61
Oceania	0.11	0.13	0.16	0.24

NOTE. The number of new cases (millions) of all cancer.

Contracts for the collection of marine invertebrates and terrestrial plants were initiated in 1986. Marine organism collections originally focused on the Caribbean and Australasia, but they have now expanded to the central and southern Pacific Ocean and to the Indian Ocean (off east and southern Africa) through a contract with the Coral Reef Research Foundation, which is based in Palau in Micronesia.[11]

Terrestrial plant collections have been carried out in more than 25 countries in tropical and subtropical regions worldwide through contracts with the Missouri Botanical Garden (Africa and Madagascar), the New York Botanical Garden (Central and South America), and the University of Illinois at Chicago (Southeast Asia), and have been expanded to the territorial United States.[9,10,11]

In carrying out these collections, the NCI contractors work closely with qualified organizations in each of the source countries. Botanists and marine biologists from source country organizations (SCOs) collaborate in field collection activities and taxonomic identifications, and their knowledge of local species and conditions is indispensable to the success of the NCI collection operations. The collaboration between the SCOs and the NCI collection contractors, in turn, provides support for expanded research activities by source country biologists, and the deposition of a voucher specimen of each species collected in the national herbarium or repository is expanding source country holdings of their biota.[11]

Letter of Collection and Collaborative Agreements

Through its Letter of Collection (LOC) and agreements based on it, the NCI invites scientists nominated by SCOs to visit its facilities, or equivalent facilities in other approved United States organizations, for 1 to 12 months to participate in collaborative natural products research. Representatives of many of the source countries have visited the NCI and contractor facilities for shorter periods to discuss collaboration. The LOC also dictates terms of the sharing of test results, benefit sharing, and use of source country resources in the event of the licensing and development of a promising drug candidate.

It should be noted that the formulation of the NCI policies for collaboration and compensation embodied in the LOC predated the drafting of the United Nations Convention on Biologic Diversity in Rio de Janeiro by some 4 years. Agreements based on the LOC have been signed with Bangladesh, Cambodia, Ecuador (AWA People's Federation), Gabon, Ghana, Laos, Madagascar, Papua New Guinea, Philippines, Sarawak (Malaysia), Tanzania, and Vietnam. Even where no formal agreement has been finalized, the NCI is committed to abiding by the terms of the LOC in every source country participating in the collection program.

With the increased awareness by genetically rich source countries of the value of their natural resources and the confirmation of source country sovereign rights over these resources by the United Nations Convention of Biologic Diversity, organizations involved in drug discovery and development are increasingly adopting policies of equitable collaboration and compensation in interacting with these countries. Particularly in the area of plant-related studies, source country scientists and governments are committed to performing more of the operations in-country, as opposed to exporting raw materials.

The NCI has recognized this fact for some 10 years and has negotiated Memoranda of Understanding with a number

Table 2. Representative Plant-Derived Drugs in Clinical Use or Development

Drug Class	Example	Source Plant	Collection/Source Region	Development Stage
Vinca alkaloids*	Vinblastine, vincristine, vinorelbine	*Catharanthus roseus*	The Philippines, Jamaica, Madagascar	Clinical use
Lignans*	Etoposide, teniposide	*Podophyllum* species	Eastern United States, Himalayas	Clinical use
Taxanes*	Paclitaxel, docetaxel	*Taxus* species	Northwest United States, Europe	Clinical use
Camptothecins*	Topotecan, irinotecan HCl	*Camptotheca acuminata*	China	Clinical use
Cephalotaxanes	Homoharringtonine	*Cephalotaxus harringtonia*	China	Clinical trials
Flavones	Flavopiridol (synthetic based on rohutikine)	*Dysoxylum binectariferum*	India	Clinical trials
Stilbenes*	Combretastatin prodrug (AVE8062A)	*Combretum caffrum*	South Africa	Clinical trials

*Several are semisynthetic analogs in use and/or development.

Table 3. Representative Microbial-Derived Anticancer Drugs in Clinical Use and Development

Drug Class	Example	Source Organism	Development Stage
Anthracyclines*	Daunomycin, doxorubicin, epirubicin, idarubicin	*Streptomyces* species	Clinical use
Glycopeptides	Bleomycins A_2 and B_2	*Streptomyces verticillus*	Clinical use
Peptolides	Dactinomycin	*Streptomyces* species	Clinical use
Mitosanes	Mitomycin	*Streptomyces* species	Clinical use
Rapamycins*	RAD001	*Streptomyces* species	Phase I
Staurosporins*	UCN-01, CEP-751, rebeccamycin derivatives	*Streptomyces* species	Phase I, II
Epothilones*	EPO906 (epothilone B), BMS-247550, epothilone D	*Sorangium cellulosum* (myxobacteria)	Phase I, II
Cryptophycins	Cryptophycin-52 (synthetic)	*Nostoc* species (cyanobacteria)	Phase I

*Several are semisynthetic analogs in use and/or development.

of SCOs suitably qualified to perform in-country processing and drug discovery. In considering the continuation of its plant-derived drug discovery program, the NCI has de-emphasized its contract collection projects in favor of expanding closer collaboration with qualified SCOs.

In establishing these collaborations, the NCI undertakes to abide by the same policies of collaboration and compensation as specified in the LOC. NCI assists SCOs in establishing their own cell line prescreens, provides secondary in vitro and in vivo testing, and will collaborate in the development of any SCO invention which meets the NCI selection criteria. Through this mechanism, collaborations have been established with organizations in Australia, Bangladesh, Brazil (five SCOs), China (three SCOs), Costa Rica, Fiji, Iceland, Korea, Mexico, New Zealand, Pakistan, Panama, and South Africa (two SCOs).

INTERETHNIC DIFFERENCES AND PHARMACOGENETICS

Pharmacogenetics and Pharmacogenomics

Pharmacogenetics is becoming an important aspect of cancer therapeutics. It originated from the observation that variability in drug clearance was sometimes polymorphic and heritable, and it relates to the understanding of how germline genetic variation may affect interindividual differences in response to medications. In the era of genomics, the term "pharmacogenomics" has also been incorporated to relate to the studies in which information on DNA or RNA is applied to pharmaceutical research and drug discovery.[16]

The application of pharmacogenomics to oncology should consider not only the information on the genome of the germline but the genome of the tumor as well. The latter can be influenced by the growth characteristics of the tumor and the effects of drug exposure. In oncology, the goal of pharmacogenomics is to improve the therapeutic index of anticancer drugs.[17-19]

There is at least one single nucleotide polymorphism (SNP) in every 500 to 1,500 base pairs, which means that every human gene is likely to exhibit polymorphism. In practical terms, polymorphism is considered when changes in one or more base pairs (mutation) occurs with a frequency equal to or higher than 1%. Polymorphism can occur in a single SNP or in multiple SNPs (haplotype).[17,19]

Examples of Genetic Polymorphisms of Clinical Relevance

Our challenge is to identify which genetic polymorphisms are of clinical importance. One example of poly-

Table 4. Current Marine Organism–Derived Anticancer Drugs in Development

Drug Name	Source Organism (type)	Collection Region	Development Stage
Aplidine	*Aplidium albicans* (tunicate)	Mediterranean sea	Phase I, II
Bengamide analog	*Jaspis* species (sponge)	Fiji	Phase I
Bryostatin 1	*Bugula neritina* (bryozoan)	Gulf of California	Phase II
Discodermolide	*Discodermia dissoluta* (sponge)	Caribbean sea	Phase I
Dolastatin 10	*Dolabella auricularia* (mollusk)	Indian Ocean	Phase I
Ecteinascidin 743	*Ecteinascidia turbinata* (tunicate)	Caribbean Sea	Phase II, III
Halichondrin B analog	*Lissodendoryx* species (sponge)	New Zealand	Phase I
Hemiasterlin analog*	*Cymbastella* species (sponge)	Papua New Guinea	Phase I
Isogranulatimide*	*Didemnum granulatum* (tunicate)	Brazil	Phase I
Kahalahide F	*Elysia rubefescens* (mollusk)	Hawaii	Phase I, II
Squalamine	*Squalus acanthias* (dogfish shark)	Atlantic Ocean	Phase II

*Several semisynthetic analogs are earlier in development.

Table 5. Drugs Approved in Japan to Treat Cancer Since Creation of the PMDEC

Date of Approval	Drug Name	Indication
July 1997	Paclitaxel	Ovarian cancer
January 1999	S-1	Gastric cancer
February 1999	Paclitaxel	Breast and NSCL cancer
March 1999	Bicalutamide	Prostate cancer
March 1999	Gemcitabine	NSCL cancer
March 1999	Interferon-alfa	CML
March 1999	Vinorelbine	NSCL cancer
March 1999	Recombinant interleukin-2	Renal cell carcinoma
September 1999	Fludarabine	CLL
December 1999	Cisplatin	Osteosarcoma and SCL cancer
January 2000	Cytarabine (high-dose)	AML and ALL
April 2000	Docetaxel	Gastric, H&N, and ovarian cancer
June 2000	Etoposide (oral)	Cervical cancer
July 2000	Carboplatin	NSCL cancer
September 2000	Interferon-gamma	Cutaneous T-cell lymphoma
December 2000	Anastrazole	Breast cancer
December 2000	Topotecan	SCL cancer
April 2001	Gemcitabine	Pancreatic cancer
April 2001	Melphalan (high-dose)	Conditioning for BMT
April 2001	S-1	H&N cancer
April 2001	Trastuzumab	Breast cancer
May 2001	Paclitaxel	Gastric cancer
June 2001	Rituximab	$CD20^+$ lymphoma
November 2001	Imatinib (STI571)	CML

NOTE. Adapted from Fujiwara and Kobayashi.[23]

Abbreviations: CML, chronic myeloid leukemia; SCL, small-cell lung; AML, acute myeloid leukemia; ALL, acute lymphocytic leukemia; CLL, chronic lymphocytic leukemia; NSCL, non–small-cell lung; H&N, head and neck.

morphism that is relevant for patient care involves the enzyme UGT1A1, responsible for the detoxification of SN-38, the active metabolite of the topoisomerase I inhibitor irinotecan. The *UGT1A1* promoter allele was shown to vary significantly among individuals of European, Asian, and African ethnicity.[16,18,19] Furthermore, SNPs in *UGT1A1* exon 1 were identified in Japanese individuals in association with hyperbilirubinemia (resulting in Gly71Arg) and in Taiwanese individuals (resulting in Pro364Lys with unknown phenotype). In Figs 4 and 5, SN-38 metabolism and the degree of irinotecan-induced leukopenia are shown for patients according to *UGT1A1* promoter genotype.[18,20,21]

P-glycoprotein (MDR-1), an important transporter for many agents, including anticancer drugs, is also polymorphic. Genotype frequencies for the C3435T *MDR1* polymorphism

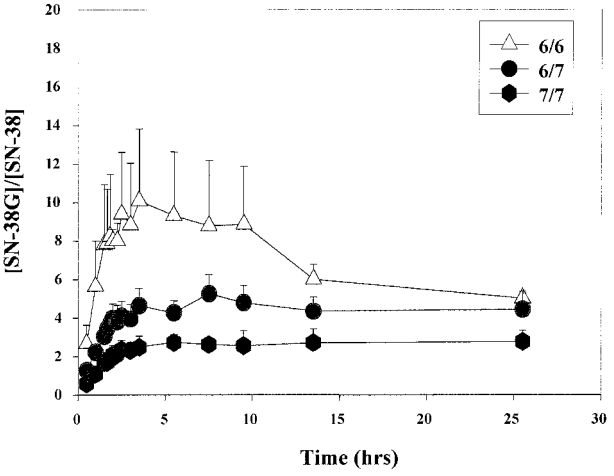

Fig 4. SN-38 metabolism in patients by genotype. Adapted from Iyer L, Das S, Janisch L, et al: UGT1A1*28 polymorphism as a determinant of irinotecan disposition and toxicity. Pharmacogenom J 2:43-47, 2002.

were described for West Africans, African Americans, whites, and Japanese. Statistically significant differences in the concentrations of nelfinavir and efavirenz in plasma and in CD4−cell count response to antiretroviral treatment according to MDR1 3435 genotype were reported.[18,19]

The enzyme thymidylate synthase (TS), the main target of the fluoropyrimidine class of anticancer agents, was also shown to exhibit a polymorphism that may have an impact on treatment outcome. Significant ethnic differences in a polymorphism in the *TS* 5'UTR have been reported.[20] In patients with colorectal cancer, a greater survival benefit was observed in individuals expressing the *TS* 5'UTR 2R/2R

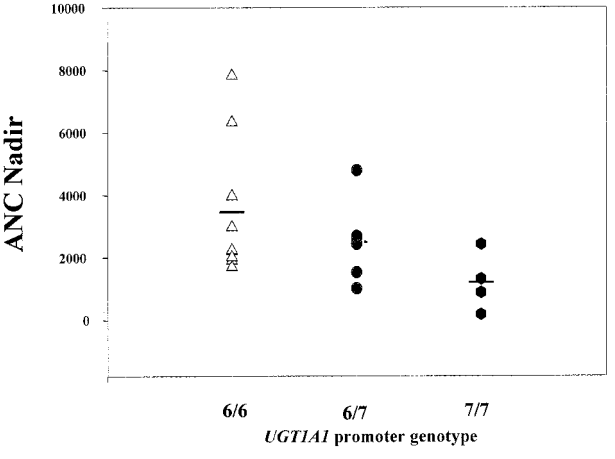

Fig 5. Irinotecan toxicity by genotype. ANC, absolute neutrophil count. Adapted from Iyer L, Das S, Janisch L, et al: UGT1A1*28 polymorphism as a determinant of irinotecan disposition and toxicity. Pharmacogenom J 2:43-47, 2002.

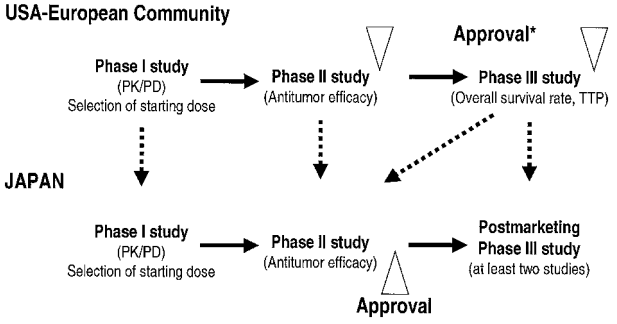

Fig 6. Anticancer drug approval process. *Marketing approval in the U.S. or Europe may be granted on the basis of either phase II or III studies (solid arrows, flow of development efforts; dashed arrows, possible routes for extrapolating data from regions; triangles, steps to official approval.)

or 2R/3R genotypes. Similar results were reported for two groups of patients receiving preoperative fluorouracil-based therapy: those with rectal cancer who exhibited the 2R/2R genotype and those with metastatic disease who exhibited the 2R/3R genotype.[19,21,22]

The data currently available suggest that interethnic variability is common, as is intraethnic variability, especially among populations of African descent. Polymorphisms may affect the pharmacokinetics (metabolism or transport) of therapeutic agents as well as their pharmacodynamics (clinical toxicity or treatment response). Although more studies are indicated, it seems that genotype patterns are more important than ethnicity on its own.[18]

ANTICANCER DRUG DEVELOPMENT IN JAPAN

In Japan, the excellent and pioneering research work of various investigators led to the discovery and development of several active anticancer drugs, including mitomycin, bleomycin, oral fluoropyrimidines such as capecitabine, and the topoisomerase I inhibitor irinotecan, all of which are routinely used all over the world. Currently, several drug discovery and development programs initiated in both academic institutions and in the pharmaceutical industry are actively engaged in the evaluation of new agents and drug combinations in various research centers, under the leadership of the National Cancer Institute of Japan.

In 1996, the Japanese Pharmaceutical Affairs Law and its related laws were amended based on the 1996 report of the ad hoc Committee for Drug Safety-Ensuring Measures. Therefore, between 1996 and 2002, the drug approval process in Japan underwent a series of important changes (Fig 6).

On the basis of these new legal requirements, strengthening of Good Clinical Practice, Good Laboratory Practice, Good Post-Marketing Surveillance Practice, standard compliance reviews, and the establishment of a special preapproval licensing system were implemented in Japan.[23,24] Between July 1997 and December 2001, the Pharmaceuticals and Medical Devices Evaluation Center approved a large number of anticancer agents for individual indications, and the speed of the review process has improved significantly (Table 5).

SINGAPORE–HONG KONG–AUSTRALIA ANTICANCER DRUG CONSORTIUM

There are several compelling reasons to promote cancer research in other parts of Asia. Although breast, colorectal, and lung cancer are common around the world, Asia has a particularly high incidence of liver, stomach, and nasopharyngeal cancer (Figs 2 and 3). Unfortunately, the pace of drug discovery for these types of cancer that are more prevalent in Asia has been painfully slow, and there is an urgent need to address this problem.

In 1998, the Cancer Therapeutics Research Group was formed, comprising the National University Hospital and the National Cancer Center in Singapore, Johns Hopkins Singapore, the Sydney Cancer Center, University of Sydney in Australia, and the Chinese University of Hong Kong. The objective of this consortium was to provide the platform for drug development in Asian and white populations, as well as to provide an Asia-Pacific database for cancer drug development.

As discussed earlier in this article, it is known that ethnicity and genotype may have an impact on the metabolism of various drugs. The classical example is amonafide, the acetylated metabolite of which was responsible for both efficacy and toxicity. As Asians are more likely than whites to be rapid acetylators, toxicity profiles differed markedly among individuals of Asian and white descent.[25]

Initial studies from the above-mentioned research consortium have demonstrated that the metabolism of docetaxel differs significantly between Asians and whites, with ethnicity appearing as an independent predictor for response and survival in patients with non–small-cell lung cancer. Ethnicity was shown to also play a role in the myelotoxicity profile in women with breast cancer receiving doxorubicin and cyclophosphamide. Other studies addressing differences in the pharmacokinetic behavior and pharmacodynamic effects of various anticancer agents are on their way.

DRUG APPROVAL PROCESS IN THE EUROPEAN COMMUNITY

The Premises

The drug approval process should be based on the premises of protecting and promoting public health through the provision of safe and effective therapeutic agents, giving patients rapid access to new therapies, facilitating the free

movement of pharmaceutical products between different regions, improving information for patients and professionals on the proper handling and use of drugs, as well as optimizing drug development and pharmaceutical research. The European Medicines Evaluation Agency (EMEA) was created in 1995 to coordinate the scientific evaluation of the safety, efficacy, and quality of medicinal products that undergo drug authorization procedures.[26]

The Centralized Procedure

In Europe, there are several procedures for that purpose, including a centralized procedure, with applications made directly to the EMEA, which results in a single marketing authorization, valid for all the European Union. This procedure is compulsory for products derived from biotechnology and optional for other innovative medicinal products.

The Mutual Recognition or Decentralized Procedure

A mutual recognition or decentralized procedure is used for products not eligible for the centralized procedure, or when applicants choose not to follow the centralized procedure but wish to get marketing authorization for a drug in two or more countries (the authorization awarded for one country is recognized by other member states). The EMEA's Committee for Proprietary Medicinal Products (CPMP) evaluates the scientific content of all applications that enter via the centralized procedure. It may also act in case the drug approval obtained in one country via the mutual or decentralized procedure is challenged in another member country.

Guidance to Pharmaceutical Companies

The EMEA also provides scientific guidance to companies regarding the type of data required for future drug approval. As of early 2002, 24 oncologic agents had been approved through the centralized procedure. Drug applications from pharmaceutical companies submitted via the centralized procedure are evaluated by two CPMP members, who prepare a final report with the input of other members and the company response to queries raised during the process.

The CPMP then recommends the drug for approval or not, and this result is published on the EMEA's Internet site. The EMEA presents its interim decision to the representatives of the member states in the European Commission and waits for their objections. If no objection is presented, the EMEA's decision is given a final approval.

In the EMEA's experience, most anticancer drugs are approved within 12 to 18 months. The United States Food and Drug Administration has an even better track record in drug approval. For instance, 15 of the cancer drugs it has approved have also been approved by EMEA and it took an average period of approximately 273 days to approve these agents. Furthermore, from 1997 to 2001, the Food and Drug Administration has subjected 18 cancer drugs to its priority review process, and its priority drug approval average was 186 days (range, 72 to 414 days).

Table 6. Examples of Intrinsic and Extrinsic Ethnic Factors Relevant to Anticancer Drug Development in Different Geographic Regions

Intrinsic Factor	Extrinsic Factor
Genetic polymorphism	Medical practice in the region
Age	Dietary habits
Sex	Tobacco use
Height	Alcohol use
Weight	Socioeconomic status
Lean body mass	Compliance with medications
Body composition	Practices in trial design
Organ dysfunction	Practices in trial conduct

ETHNIC DIFFERENCES AND OPTIMIZATION OF INTERNATIONAL ONCOLOGY STUDY DESIGN

In this discussion, an overview is presented of the principles outlined in the International Committee of Harmonization (ICH) E5 addressing the issue of ethnic factors in the acceptability of foreign clinical data. Extrinsic differences between oncology practice in Japan and the United States are summarized as an example. Suggestions are provided for optimizing the design of international studies in oncology based on an understanding of the ethnic differences between two regions.[24]

The ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use addresses the issue of ethnic factors in the acceptability of foreign clinical data in its E5 document. The purpose of the guidance document, summarized below, is to facilitate the registration of medicines in the United States, Europe, and Japan by recommending a framework for evaluating the impact of ethnic factors on a drug's effect (Table 6). In addition, the E5 describes the use-bridging studies to allow extrapolation of foreign clinical data to a new region.

To be accepted as a basis for approval in a new region, the foreign clinical data package must meet all the regulatory requirements of the new region. If it does, the clinical data package is complete, and the only issue is whether these data can be extrapolated to the population of the new region.[24]

When a regulatory authority or sponsor, in possession of a complete clinical package, is concerned that differences in ethnic factors could alter the efficacy or safety profile of a drug in the new region's population, the sponsor may be asked to generate a limited amount of clinical data in the new region in order to "bridge" the existing clinical data to

the new population. Knowledge of a drug's pharmacokinetic and pharmacodynamic properties and their relationship to effectiveness and safety may be required in designing a bridging study.

Characterization of a drug as "ethnically insensitive" usually facilitates extrapolation of data from one region to another. A lack of metabolism or active excretion, a wide therapeutic dose range, and a flat dose-response curve may reduce the likelihood of ethnic differences. Conversely, clearance by an enzyme showing genetic polymorphism and a steep dose-response curve may accentuate ethnic differences. The clinical experience with other members of the drug class in the new region will also contribute to the assessment of the medicine's sensitivity to ethnic factors.

Intrinsic and Extrinsic Ethnic Factors

In assessing the need for a bridging study, investigators should be aware of intrinsic and extrinsic ethnic factors. Extrinsic factors are those associated with the environment and culture. These tend to be less genetically and more culturally and behaviorally determined. Examples include medical practice, diet, tobacco use, alcohol use, socioeconomic status, compliance with medications, and practices in clinical trial design and conduct. Intrinsic factors assist in defining and identifying a subpopulation. These include genetic polymorphism, age, sex, height, weight, lean body mass, body composition, and organ dysfunction (Table 6).

Bridging Studies

A bridging study is defined as a study performed in a new region to provide pharmacodynamic or clinical data on efficacy, safety, dosage, and dose regimen in the new region. Bridging studies allow extrapolation of the foreign clinical data to the population in the new region. When the regulatory authority requests a bridging study, or when the sponsor decides, on its own, to conduct one, discussion between the regional regulatory authority and sponsor is encouraged, to determine the design of the study. The relative ethnic sensitivity will help determine the need for and type of bridging study.

If two regions are ethnically dissimilar and the drug is ethnically sensitive, but extrinsic factors are generally similar and the drug class is familiar in the new region, a controlled pharmacodynamic study reflecting relevant drug activity may suffice. In this case, simultaneous evaluation of pharmacokinetic data is encouraged.

A controlled trial with clinical end points may be required if doubt exists about the dose selection, if there is little experience with the acceptance of controlled clinical trials performed in a foreign region, if medical practice differs substantially between the two regions, and/or if the drug class is unfamiliar to the new region. With respect to safety concerns, a trial to assess efficacy, such as a dose-response study, could be powered to address rates of common adverse events. Alternatively, a separate safety study could be required if concerns about reporting differences exist, an index case of a serious adverse event is present in the foreign clinical data package, or the efficacy bridging study is of insufficient size to provide a satisfactory safety evaluation.

An understanding of pharmacokinetics, pharmacodynamics, and dose response early in the development program may facilitate the determination of the need for bridging data. Candidate medicines for global development should be characterized as ethnically sensitive or insensitive during the early phases of clinical drug development.

Extrinsic Ethnic Differences in Oncology Between Japan and the United States

Although intrinsic factors have a role in determining differences between populations in two different regions, extrinsic differences can be substantial and should be carefully assessed. One example of extrinsic ethnic differences in oncology is provided by Japan and the United States.[23,24]

Cancer epidemiology differs between the two regions, with gastric and hepatocellular cancer being far more common in Japan than in the United States. Experiences in diagnosing and treating these different cancers may have an impact on medical decision making and oncology care delivery. In the United States, medical oncologists are the primary providers of care for patients with cancer. Medical oncologists are usually also responsible for coordinating patient care with other specialists, such as surgeons and radiation oncologists.

Furthermore, the NCI has provided a framework for oncology drug development in the United States over three decades, with cooperative groups contributing to this effort. In Japan, surgeons, gastroenterologists, and other subspecialists have been the primary providers of care for cancer patients. Recently, an interest in developing medical oncology as a discipline has emerged along with the recent development of Japanese clinical trials cooperative groups performing clinical trials consistent with practices accepted in the United States and Europe.[24]

Differences exist between the two countries with respect to end points used for the approval of cancer drugs. In Japan, registration trials have focused on response rates as a clinical end point. Trials submitted for approval in the United States have focused on clinical benefit end points, such as survival or relief of a disease-related symptom.[24]

Doses of oncology drugs used in Japan have generally been lower than those used in clinical trials in the United States. Although differences in recommended doses may reflect intrinsic ethnic differences, they could represent

extrinsic factors, such as differences in the acceptance of toxicities by patients and physicians.[23]

Optimizing International Study Design

In designing international trials where ethnic factors may affect results, sponsors should attempt to avoid primary end points that could have strong cultural or societal influences. End points that have the potential for investigator bias or subjectivity should be avoided. Improvement in overall survival is an end point that has universal acceptance in oncology. It minimizes bias and potential for subjective interpretation and represents evidence of clinical benefit.

Reliance on end points that represent subjective and cultural evaluations of quality of life or symptom benefit should be minimized. An end point that relies on a radiologic assessment (ie, tumor response, time to progression) also raises concerns because technical assessments and expertise (types of imaging, subjectivity in radiograph reading) can vary between regions and between individual centers in the same region or country. Blinding of trials should be encouraged when feasible. Study sites should have the capacity to enroll sufficient numbers of patients and offer subsequent therapy and supportive care that meets international standards.

OPPORTUNITIES AND CHALLENGES FOR THE GLOBAL PHARMACEUTICAL INDUSTRY

The Opportunities

This is a time of significant opportunities and challenges for the global pharmaceutical industry. Recent biomedical science and technologic advances present unprecedented opportunities for the development of more effective therapies for malignancy. New targets for anticancer agent development are rapidly emerging in the postgenome era, and improvements in protein structure determination, combinatorial chemistry, and high-throughput small-molecule screens may accelerate the generation of new agents to be studied in the clinic. The long-unfulfilled promise of more efficient data collection and transmission through electronic data capture may yet improve the technical aspect of the conduct of clinical research.

The Challenges

The pharmaceutical industry itself is dealing with significant challenges. Recent years have seen consistent increases in research and development costs, without to date an accompanying increase in productivity as evidenced by new molecular entities being submitted for regulatory review. Meanwhile, development times have lengthened, thereby shortening the length of time an approved agent will bring financial returns before patent expiration.

Development risk has not been decreased yet by the introduction of new technologies; a distressing number of agents still fail during late-stage clinical development. Furthermore, an increasingly conservative regulatory climate is being encountered generally by the industry, although less so related to oncology products.

Significant challenges to traditional intellectual property protection are being encountered globally, particularly with expensive agents for specialty indications. Even after regulatory approval, an increasingly difficult reimbursement climate is presenting another level of gatekeeping with respect to drug availability to patients. Once patent protection expires, generic erosion is swift.

All of these challenges mean that to flourish, the industry must learn to develop more effective anticancer agents more rapidly, with fewer resources and with the risk of development failure minimized. Many of the new technologies referred to previously can be harnessed to address this goal, but certainly one area in which significant gains can be achieved, and where use of clinical research resources globally can contribute, is in the area of clinical trials involving new anticancer agents.

Clinical Trials Strategies

The range of clinical trials necessary in the clinical development of a new anticancer agent is a familiar one. The initial trials traditionally have been designed to answer questions regarding toxicity and pharmacokinetics. As the nature of anticancer agents being developed has evolved to agents aimed at specific biologic targets, these early trials have evolved to focus on answering "proof-of-concept" questions in addition to the traditional toxicity and pharmacokinetic goals.

Incorporation of Pharmacodynamic End Points

Now when a trial is complete, questions should be answered as to whether the agent has accomplished its biologic goal with respect to interaction with its intended cellular target. Furthermore, the trial should allow correlation of pharmacokinetic measurements with pharmacodynamic end points (eg, biologic or clinical measurements of some drug-related effect). These early trials ideally should involve patient populations with tumors in which the intended target is present and pathophysiologically relevant.

All of these characteristics imply that early development trials are becoming more complicated and more resource-intensive, involving more carefully selected and biologically profiled patients. They are best conducted in centers with an established infrastructure for the collection of the

necessary specimens, and sometimes the performance of specialized imaging techniques.

Registration-Directed Studies

Later development clinical trials conducted in the context of a global registration-directed development program are designed to answer clinically relevant hypotheses related to effectiveness (such as response rate, time to progression, and survival) or toxicity, often comparative to current standards of treatment. Conduct of these large, often global registration trials also gives a broad range of oncologists experience with the agent and increases the total base of patients treated.

Traditionally registration-directed clinical development conducted by global pharmaceutical companies has been concentrated in the United States and Europe, for obvious reasons related to location of the companies and their research staff, location of experienced investigators and institutions, and locations of the major ultimate markets for the therapeutic agents.

Clinical Trials in New Geographic Areas

The initial drivers for conducting trials in the rest of the world related to needs to access new patient pools in order to speed accrual, decrease costs, or meet local regulatory requirements. The relative activity in this respect has varied greatly among companies; clinical research organizations have been aggressively opportunistic in creating operations in newer areas. Nevertheless, the bulk of the initial trials have been late-stage development trials, and sometimes they are very marketing-driven, rather than registration-driven.

This situation is rapidly changing, for a series of reasons. The increase in the number of new anticancer agents in development and the increase in the complexity of the new trials have increased the need for more patients entered onto trials and for a greater range of investigators and institutions capable of studying these patients.

Meanwhile, there has been a great increase in the interest in new anticancer agent clinical development globally, and many new centers have emerged—in Southeast Asia, in Central and South America, and in Central and Eastern Europe— capable of conducting early development clinical trials. Furthermore, there has been an increasing recognition of the importance of ethnic diversity, sex, and age in drug development, and therefore an increasing need to study a representative range of individuals during the registration phase.

As the clinical development teams of pharmaceutical companies make decisions regarding global registration-directed clinical trials, they consider a number of questions as they decide which countries and centers to include in the development plan for a particular agent in a given indication. These questions relate to how common the indication is, whether treatment approaches are uniform or differ around the world, whether primary therapy is involved, the nature of approved or utilized standard therapies, the documented magnitude of benefit of these therapies, the expected magnitude of benefit of the new therapy, and considerations related to expected toxicities from the new as opposed to the standard therapies.

The answers to these questions will determine the number of trials necessary to accurately profile an agent, whether comparator arms are necessary, and if so, whether the same or different comparator arms will be used in different parts of the world. These characteristics in turn determine whether a single global trial or parallel regional trials are preferable.

Issues related to the indication also determine the nature of the end points necessary for a registration trial and the attendant complexity and therefore resource intensity of the trials, particularly the need for accompanying studies, such as pharmacokinetic, pathologic, genomic or proteomic, pharmacogenetic, and imaging studies.

Increasingly, it is also becoming necessary for registration in some countries to conduct cost-benefit or quality-of-life studies during the registration process. Cost, rapidity of clinical trial approval, level of clinical trial infrastructure the company has in a particular country or region, the need for patients of particular ethnic background—all of these play a role in determining which countries, and which sites within countries, will participate in a global registration program.

The ICH

Generally, companies today have a single, global, registration-directed clinical trials development program. Conducting clinical trials toward registration in countries signatory of the ICH means that there are agreed standards for the conduct of clinical trials and on the registration package's general content and format.

However, little is standardized beyond these criteria. In particular, there exists no general agreement on criteria for approval, so that a final global development strategy must often encompass widely divergent opinions from different regulatory bodies. Furthermore, as indicated earlier, regulatory approval increasingly is being followed by reimbursement approval, and some notable disconnects recently have illustrated the difference between these two levels of gatekeeping.

Imatinib as an Example

The power of international cooperation among clinical investigators to rapidly generate a body of clinical evidence leading to rapid registration of an effective antimalignancy agent has recently been demonstrated in the development of the drug imatinib (Glivec, Gleevec; Novartis AG, Basel, Switzerland) for chronic myeloid leukemia (CML). After

rapid dissemination of the initial phase I clinical trial results to the medical community and the public, all of the world's cooperative groups engaged in clinical trials of CML cooperated in the conduct of a front-line trial in newly diagnosed patients.[27]

Within several months, more than 1,100 patients were entered onto the imatinib trial, and the initial results presented at the 2002 annual meeting of the American Society of Clinical Oncology represent a landmark in both a change in the natural history of CML and in the conduct of global clinical development. Furthermore, an unprecedented level of cooperation among major regulatory agencies has led to the rapid approval of this agent in the second-line setting globally. While the clinical development program was no less complicated than usual, the extent of international cooperation by patients, investigators, and regulatory agencies greatly accelerated the general availability of the agent.

In conclusion, many opportunities exist to utilize the growing interest and capability of investigators and institutions globally to accelerate the pace of anticancer development generally. General agreement on end points acceptable for registration for specific indications would greatly improve the global clinical development situation. Similarly, general acceptance of a standard data package and introduction of standard electronic case report forms and programming tables might greatly improve the efficiency of clinical trial conduct internationally.

The many advances in biomedical science and technology present unprecedented opportunities for new therapeutics development in cancer, and these opportunities can be best pursued through international cooperation that utilizes the best minds and energies of investigators, the goodwill and cooperation of patients, and the best scientific and treatment resources which can be identified, wherever in the world they exist.

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