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ORIGINAL ARTICLE

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Cooperative oncology groups in Japan: Experience from the Japan Adult Leukemia Study Group

Abstract To ensure reliable statistical analysis in clinical trials, a large number of patients is required and therefore multicenter cooperative studies are indispensable in clinical oncology. However, both in the field of oncology and other fields of medicine, well-functioning clinical study groups are rare in Japan. In this review, the reason why multicenter cooperative study groups are difficult to organize in Japan is analyzed. Subsequently, the experience of a self-supporting and successful cooperative study group, the Japan Adult Leukemia Study Group, is reviewed. Finally, in the absence of significant financial support and thus no financial benefit for participating institutions, how to organize a cooperative study group successfully is discussed.

Key words Clinical study · Multicenter cooperative study · Clinical study group · Japan Adult Leukemia Study Group · Internet

Introduction

Several factors are important in conducting a scientifically valid clinical study: the number of patients studied must be sufficient for statistical analysis; and the study should be well designed and beneficial to society. In addition, clinical trials should be conducted according to Good Clinical Practice guidelines, i.e., they should be ethical and scientific, be approved by the institutional review board, and be conducted only after informed consent has been obtained from patients. Participating physicians should accrue patients prospectively and consecutively, and strictly but safely follow the study protocols. Of these factors, the number of patients is a key factor in any scientific study.

When comparing a new therapy regimen, B, with an existing regimen, A, in a prospective randomized study, statisticians require that a large number of patients be accrued. For example, for a presumed 10% difference in outcome between the 2 regimens at a P value of 0.05 with power of 0.8, eg, complete remission rates of 80% vs 70%, 293 patients must be accrued to each arm for a total of 586 patients. If the presumed difference between regimen outcomes is 5%, the number of patients required in each arm will be 1251 for a total of 2502 patients. Therefore reliable scientific evidence in clinical oncology requires that a large number of patients is accrued to trials, meaning that multicenter cooperative studies are indispensable.

Cooperative oncology study groups after World War II

From the end of World War II until the 1980s, US National Cancer Institute-sponsored oncology groups such as the Southwest Oncology Group, Eastern Cooperative Oncology Group, Cancer and Leukemia Group B, North Central Cancer Treatment Group, Pediatric Oncology Group, Children's Cancer Group, National Surgical Adjuvant Breast and Bowel Project, Gynecological Oncology Group, Brain Tumor Cooperative Group, and Radiation Therapy Oncology Group, as well as the European Organization for Research and Treatment of Cancer, and the Medical Research Council in the UK were leaders in the study of clinical oncology. The evidence obtained from their studies served as the standard in cancer therapy. However, in the mid-1980s, the results of German multicenter clinical trials, particularly in the field of leukemia chemotherapy, started to be reported, and Germany soon became a leading force in clinical oncology.

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Table 1 Comparison of the anticancer campaigns in Japan and Germany

	German Krebsbekämpfung	Japanese 10-year anticancer strategy
Year started	1979	1984
Field	Clinical and basic	Basic and infrastructure
No. of statistical centers	5	0
Scope of cooperative studies	Nationwide	6–12 institutions
Projects	Disease oriented	Disease oriented
Group support	Yes	No
Term per project	4–7 years	1–3 years

The Krebsbekämpfung in Germany

Since Germany and Japan share a similar post-World War II history, Germany's sudden emergence as a leader in this field is of interest to Japanese oncologists. Thus the author visited Bonn, Berlin, Frankfurt, and Münster, the initials of the latter 3 of which form the name of the BFM group which studies childhood leukemia.

The reason for the sudden German success in leukemia chemotherapy is as follows. Germany started an anticancer campaign in 1979 with grants from the Bundesministerium für Forschung und Technologie and 2 other ministries. The first priority was to determine the best strategy by which to bring cancer therapy in Germany up to international standards. This proved to be the establishment of biostatistical centers and supporting nationwide disease-oriented multicenter cooperative study groups. Therefore 5 biostatistical centers were established at 5 universities. A typical center consisted of 7 personnel: one physician, one biostatistician, one computer engineer, 2 data managers, one clerk, and one secretary. Disease-oriented groups in areas including childhood leukemia, adult acute myeloid leukemia (AML), adult acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), breast cancer, etc were established, and each group signed a contract with a biostatistical center.

Ten-year anticancer strategy in Japan

In Japan, a 10-year Anticancer Strategy was initiated in 1984 with grants from the Ministries of Health and Welfare (MHW), Education and Culture, and Science and Technology. However, the main aim of this strategy was to explore the mechanism of tumorigenesis and to build up the clinical oncology infrastructure. Although many clinical projects were launched, they were mostly on a small scale, no statistical centers were established, and no oncology groups were supported. In Germany, more money was granted to clinical studies than to basic science, but in Japan the reverse was true (Table 1). The total amount of Grants-in-Aid for Cancer Research from the Japanese MHW was ¥1250 million in 1975, ¥1600 million in 1981, ¥1850 million in 1992, and ¥1850 million (approximately US$ 14.5 million at current exchange rates) in 1996.

Japan entered the second term of the 10-year Anticancer Strategy in 1994, but the basic strategy remained the same: no clinical study group is officially supported and no independent statistical center has been established except for the Japan Clinical Oncology Group (JCOG) and its statistical division. However, the JCOG is not an officially approved group name; its official Japanese name is the project for the "Study of multimodality therapy of solid tumors." The 1996 annual report on the MHW Grants-in-Aid for Cancer Research published by the National Cancer Center of Japan rarely mentions the name JCOG [11].

Difficulties in organizing multicenter cooperative groups in Japan

Well-functioning clinical study groups are rare in Japan, both in the field of oncology and other fields of clinical medicine. The reasons why multicenter cooperative groups are difficult to organize in Japan are outlined below.

First, there is the so-called school clique. Japan was and still is a provincial society, and this holds true even in academia. Most Japanese still lack an international perspective, democracy has not been fully achieved, and egalitarianism is not firmly rooted in society. Therefore the medical profession continues to be controlled by elderly "big bosses." One example of this is that authorship of reports of cooperative clinical studies, which are generally sponsored by the pharmaceutical industry, is often shared by department heads, even when they have had little involvement in the study.

Probably the main reason why cooperative groups are difficult to organize in Japan is a poor understanding of the necessity for cooperative study groups by the organizations awarding grants for clinical oncology, ie, the MHW and the National Cancer Center Japan.

Japan Adult Leukemia Study Group

Should we wait until society changes? The answer is no, because by waiting Japan will fall far behind the rest of the world and never be able to establish a system of evidence-based medicine. Therefore the Japan Adult Leukemia Study Group (JALSG) was founded in 1987 as a self-supporting group of 14 institutions. The group later received indirect support through a Grant-in-Aid for Cancer Research from the MHW, but has never solicited donations from the pharmaceutical industry.

Considering the aforementioned reasons for the difficulty in establishing cooperative study groups in Japan, the rules governing JALSG were established before the group was formed. It was agreed that JALSG should operate democratically, conduct clinical studies of high quality and to international standards, write protocols after free and extensive discussion among members, and report its results only in major international journals. It was further agreed that eligible patients would be accrued consecu-

Table 2 Operating cooperative groups successfully in the absence of any expectation of financial benefit

1. Share recognition of the importance of cooperative studies
2. Design protocols through general discussions
3. Secure high-quality medical skills and facilities
4. Operate the group democratically
5. Select the first author of any publication democratically
6. Select coauthors from among actively participating investigators, not from institution chairs
7. Complete patient accrual in a short period, preferably 2–3 years

tively, protocols observed strictly, the first author of papers selected democratically, coauthors chosen from among actively participating investigators and not from among institution chairs, etc.

Fortunately, the results obtained from the group's studies, including those from the cooperative studies performed by the project team supported by a Grant-in-Aid for Cancer Research from the MHW, have been published in major international journals such as the *New England Journal of Medicine, Blood, Journal of Clinical Oncology, Leukemia, British Journal of Haematology, Annals of Internal Medicine*, etc [1–10, 12–24]. After observing these activities, realizing the necessity for cooperative studies, and particularly at the urging of young investigators, many institutions have voluntarily joined JALSG, which now comprises 61 institutions with >150 affiliated hospitals, including 45 universities, 5 cancer centers, and 11 major general hospitals. JALSG covers around 20–25% of adult leukemia patients in Japan. However, since there are 80 medical schools in Japan and 35 of them do not belong to any clinical study group, JALSG is still far from being a nationwide cooperative study group.

JALSG has conducted 12 studies to date: AML87, which included 265 patients; AML89, with 341 patients; AML92 with 994 patients; AML95 which has accrued 470 patients and is ongoing; ALL87 including 121 patients; ALL90, which included 184 patients; ALL93 with 291 patients; ALL9 7 and APL97, which have just started; CML88 with 170 patients; CML91 including 92 patients; and CML95, which has accrued 148 patients and is ongoing. At present, approximately 30 patients with AML, 10 patients with ALL, and 5 patients with CML are being accrued monthly.

Funding and organization of JALSG

The funding of JALSG is far from satisfactory. Each institution pays an entry fee of ¥150,000 and an annual membership fee of ¥30,000. In addition, the group currently receives a Grant-in-Aid of ¥25,000,000 annually from the MHW. However, this is not direct support for the group, but is a grant for a project to establish a standard therapy for leukemia in Japan. The project team consists of only 12 members chaired by Ryuzo Ohno; the project will continue for 3 years from 1997, and it is hoped that it will be extended for a further 3 years if the results are satisfactory. A one-time grant of ¥2,090,000 for the computer database was received from the Ministry of Education and Culture in 1997.

JALSG has a steering committee consisting of 61 members, one from each participating institution, and several subcommittees working in areas such as AML, ALL, CML, acute promyelocytic leukemia, myelodysplastic syndrome, leukemia in the elderly, supportive therapy, pathology (central review committee for diagnosis), chromosome analysis, membership qualification and quality control, bone marrow transplantation, and networking. JALSG does not have a dedicated statistician, and statistical analysis is done mainly by staff at a statistical center or by the chief investigators of each project with help from consultant statisticians.

Since May 1997, patient registration, randomization, and case reporting have been done via the Internet. The system was designed by the Information Processing Center, Hamamatsu University School of Medicine, and operated by computers at this center. Additionally, when subcommittees design protocols, discussion is frequently done using a groupmail e-mail system. The use of technology of this kind to conduct a multicenter cooperative study efficiently is essential because the funds to hire sufficient personnel are not available.

Benefits of multicenter cooperative clinical studies

Multicenter cooperative clinical studies can offer: 1) prospective randomized studies involving the numbers of patients necessary to produce reliable evidence; 2) scientific statistical analysis of the data; and 3) objective evaluation and reliable results. In addition, the results can be regarded as generalized nationwide outcomes. Thus cooperative study groups are a prerequisite to create evidence-based medicine in clinical oncology.

When little financial support is granted and thus no financial benefit can be expected by participating institutions, how can cooperative study groups be successfully operated? The members must all recognize the importance of cooperative studies. The group should design protocols through general and free discussion, thus enabling the participating members to feel that the study is their own and not a prepared one. Members should make every effort to secure high-quality medical skills and facilities to produce better results, which consequently encourage and motivate participating members. The group should be operated democratically. When the results are published, the first author should be selected democratically, coauthors should be selected from actively participating investigators, and more than one coauthor should be chosen from institutions that contribute many patients. At least in Japan, patient accrual must be completed over a short period, preferably within 2 or 3 years, because it is difficult to prevent investigators from using the interesting new therapies which are reported and widely disseminated because information is so easily obtained in today's society (Table 2).

The results of clinical studies are primarily a function of the financial resources available, as are those of basic science. Therefore not only the motivation and enthusiasm of clinical researchers, but also financial support and scientific infrastructure are indispensable if high-quality scientific clinical studies are to be performed. However, if sufficient financial support is not available, researchers should make efforts to organize cooperative study groups. I believe that no matter how difficult it may be, if we keep pushing a door will eventually open.

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