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How Do Cancer Researchers Perceive the Future of Cancer in Asia?

Cross-boundary Cancer Studies at the University of Tokyo: Asia as a Partner for Japan

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LECTURER PROFILE

Masahiko Nishiyama has currently served as Professor of Department of Molecular Pharmacology and Oncology, Gunma University Graduate School of Medicine where he teaches and does research on the Translational Cancer Research since 2012. He received his MD and PhD from Hiroshima University in 1987 and began work as Research Associate at the Department of Surgery, Research Institute for Radiation Biology and Medicine, Hiroshima University from 1987 to 1994. After he worked at the Molecular Pharmacology, Insitut de Cancerologie et d'immunogenetique, Vileljuif, France from 1988 to 1990 and was Lecturer at the Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University from 1994 to 1996, he held appointments as Professor working in various disease areas at Biochemistry & Biophysics, and Translational Cancer Research, Research Institute for Radiation Biology and Medicine, Hiroshima University from 1996 to 1907. He joined the Translational Research Center, Saitama Medical University International Medical Center in 2007 and was subsequently appointed as Professor/Director at the Research Institute for Development of Therapeutics, and the Division of Disease Control in the Research Center for Genome Medicine, Saitama Medical University from 2007 to 2012. Concurrently, he served as Chief Director of Japanese Society of Clinical Oncology in 2010 and Chairperson of Federation of Asian Clinical Oncology in 2012.

ASIA AS A PARTNER FOR JAPAN

In today's world, when considering cancer it is essential for us to recognize the disease not within the confines of Japan, but in an Asian and global context. Cooperation with other Asian countries and joint development and research are critical if we are to maintain medical benefits for patients in Japan over the long term. Although Japan has until now taken a leading role in cancer treatment in Asia, the reality now is that times are changing significantly. In terms of cancer treatment Asia is now a lifeline for Japan.

Background Leading up to the Formulation of the Cancer Control Act

The awareness of people today has changed. From about a decade ago we physicians began to hear opinions and criticisms with regard to cancer treatment. There were various criticisms leveled at the system in Japan, such as 'There are no specialists in cancer treatment in Japan,' 'Standard drugs that are used overseas cannot be used in Japan', and 'There is no reliable information'. This demonstrates that the cancer treatment we had provided and were providing until then was not meeting the needs or satisfying the public and patients. Opinions such as these were the catalyst for a fundamental review of cancer treatment in Japan and finally, 20 years after the USA, legislation relating to cancer, namely the Cancer Control Act, was included in the Statute Books of Japan.

Although the Cancer Control Act was passed unanimously by all members of both Houses of the Diet, it was not formulated on the basis of advice from doctors and medical associations, but rather as a piece of lawmaker-initiated legislation that was based on passionate petitions from members of the public and patients. This was a great embarrassment for those whose lives and careers are based around cancer treatment. Factors that explain why it was not possible for specialists in the cancer field to formulate such legislation lie in the idea behind it.

The basic ideas of the Cancer Control Act are clearly set forth. First, to promote specialized, multidisciplinary and comprehensive cancer research and to disseminate the results of research. Secondly, to raise cancer treatment standards. Thirdly, to establish a system that provides medical cancer care in which the treatment is selected according to the situation of the patient and respect paid to their own intentions. These are also extremely self-evident and natural desires. We are now in the sixth year since the Cancer Control Act was passed. The first 5-year basic plan for cancer control called for the establishment of core cancer treatment hospitals nationwide, the establishment of a system for medical specialists, the standardization and even distribution of cancer treatment and the promotion of new medical research and development, among other measures, which have largely been achieved, but in terms of tackling cancer they have been 5 years in which efforts have concentrated on responding to the acute stage of the disease and providing symptomatic treatment. From now it will be essential to sit down and engage in fundamental discussions on the challenges that exist, and clearly identify outputs and outcomes. It is regrettably the case that as yet there has not been any attempt to engage in the discussions that are critical for significantly raising the standards of cancer treatment in Japan.

Locating the Issues

Is it sufficient to leave the creation of a social strategy for overcoming cancer purely to legislators and governments? Is it acceptable for specialist groups such as medical associations to remain silent and not propose specific strategies or future-oriented plans? The answers to these questions are clear: No! Asia will be a very important player in discussions on such issues when actions are eventually initiated.

Before discussing cancer treatment in Asia, I would first like to discuss two issues that cancer treatment currently faces.

The first of these issues is the unease and mistrust that arises from a lack of information and awareness about cancer treatment. The second issue is the actual physical and scientific environment for medical care, including medical facilities, equipment technologies and drugs. Unless we first address these issues it will be impossible to arrive at a solution to the issue of cancer overall.

When presented with a diagnosis of cancer, almost all patients find that their minds go blank. They face cancer and the implications it brings, knowing that we are in an era in which one in two people will develop cancer and one in three will ultimately succumb to the disease. To be dispassionate or unconcerned about this fact serves only to create a lack of understanding, which leads to unease and mistrust in medical treatment. Only when people do not treat cancer as somebody else's problem and start to take an interest in cancer before it develops, can we hope to improve cancer treatment.

For example, when asked the question 'What is cancer?' hardly any people can provide a response. Cancer could be said to be another part of you that has been created inside you. Most cancers are created by the bodies of the people that develop cancer.

It is our responsibility as medical practitioners to provide correct information to patients about cancer and also to provide a broad range of information to the general public. However, from the patient's perspective it is of crucial importance that this information is accurately understood and accepted.

How does cancer develop? The human body is like a blueprint that is created from deoxyribonucleic acid (DNA) and is copied on countless occasions based on this blueprint. Cells are regenerated and created in the same place in an ongoing process of replacement. Although it is not possible for an eyeball to be created in the stomach, on occasion the copy function of the body breaks down and due to stimuli such as ultra-violet rays and tobacco the original blueprint is damaged. However, as it would not be possible for the human body to remain viable if the damage were not repaired, all living organisms have a capacity for implementing such repairs. If DNA damage occurs (i.e. a mistaken copy function occurs), it is repaired. This repair mechanism is constantly in operation, but if DNA is damaged on frequent occasions it gradually loses the capacity to repair. This causes acceleration towards the development of cancer cells and the brakes (i.e. the repair system) no longer work, resulting in cancer. It can therefore be understood that cancer is a genetic disease.

In actual fact there are statistics in Japan that show that >50% of people with cancer live for >5 years. There is tremendous psychological significance in knowing that although cancer is a very difficult disease, it is not necessarily incurable. Furthermore, correct recognition with regard to the condition of the disease and the realities of medical care make a tremendous contribution to selecting treatment that is continuous and provides satisfaction to the patient.

Treatment of cancer with drugs has a relatively short history of 50–60 years. Where once the treatment method was a course of poisonous gas, over the years dramatic developments have been made in treatment methods. In 5 years' time we may be able to expect that there will be further treatments that will extend life or cure cancer. Hope creates continuity and advances in treatment.

Advances in genomic medicine have had a significant impact on advances in cancer treatment in recent years. Ribonucleic acid (RNA) is created from DNA, and the human body is composed of proteins originating from RNA. If it is possible to find abnormalities in this process it should be possible to find the causes of disease. Accordingly, if we can find the causes of diseases we can then set about creating drugs to

address the causes. Today we have reached a point where it is possible to exhaustively analyze 3 billion bases of DNA in two-and-a-half days, and where 23 000 genes can be analyzed in a short time. We are heading towards an era in which analysis of an individual's DNA could be used to pinpoint the best drugs to treat that person.

There are many people who believe that cancer is an agonizingly painful disease. However, great advances have been made in pain management and we have reached a point where the implementation of pain relief treatment is able to be implemented as soon as a cancer diagnosis is made. Information such as this needs to be correctly understood and greater awareness promoted.

There are also many people who believe that the treatment for patient is determined by doctors, without any consultation with patients. Although it depends on the condition, it is no longer the case that treatment is decided in hospital without consultation. First of all doctors are likely to recommend the advantages of standardized treatment that have a proven track record. If the standard treatment does not work, they are then likely to recommend moving to participation in a clinical trial. If a patient wishes to take part from the beginning of his/her treatment in a clinical trial then it may also be possible to skip the standard treatment. It is now patients who select their treatment. Clinical trials are also organized based on proper methodologies and therefore treatment is selected on the basis of evidence.

Modern Medical Treatment is Collective, Transparent and Science Based

No matter how excellent a single doctor may be today, there is no one who would be arrogant enough to believe that they could resolve all conditions themselves. To provide the best possible treatment to patients doctors must read upwards of 200 specialist papers, many of them in English, in a single month. What is more, given the fact that medical journals are published around the world, doctors today must select what they consider to be reliable papers from among the 20 000 different medical-related publications available, and read these. To graduate from medical school an undergraduate student is expected to read a minimum of ~11 161 pages annually. In terms of the numbers of diseases and conditions that have been identified, there are >30 000. In addition, there are >15 000 types of medicine it is possible to prescribe, the number of which continues to increase by >250 new drugs each year. Given this background, any doctor who professes that he or she can deal with everything in all aspects of medicine his or herself is not telling the truth. It is simply not practical for a single doctor to attempt to tackle all the new developments in medicine in addition to the heavy daily workload related to medical examinations.

With regard to how medical care and treatment is practiced in reality, efforts are being made to collate the results of clinical trials, identify the treatment that would be in the best interests of the patient and advance diagnosis and treatment on the basis of results that have been evaluated by experts. This is what is known as evidence-based medicine (EBM). What is needed is doctors who seek to work as a member of a team in closely examining evidence. Years ago medicine was considered an art, but today it is firmly positioned in the realms of science. The basis for medical care in the 21st century is for medical practitioners to share knowledge and technologies, and to work as a team in providing medical care that is convincing and effective.

Difficulty for Patients in Understanding the Risks of Medical Treatment

There is another truth that I would like to share with you and have you understand. All medicine brings with it a certain element of risk. For example, take the case of a pregnant mother who came to an obstetrics and gynecology clinic. Both the mother and the unborn child were dangerously ill and the doctor was forced to choose which life to save, faced with the reality that it would be impossible to save both. The doctor therefore made the difficult decision to save the mother. What happened after that was that the doctor was sued by the mother, who wanted to know why the child could not have been saved as well. Doctors are not gods. There is no perfect medical treatment in this world and all medical care brings with it an element of risk. Just as everyone's faces are different, each person will have a different reaction to even the same medicine. If everyone realized this fact it is likely that it would help medicine to progress further. Treatment is something that is decided by the patients themselves, but there is no treatment that is absolutely guaranteed to work. The current situation is one in which the treatment is chosen that is deemed to be the best option based on the results of EBM. I believe that simply by making patients aware of this reality would help to assuage their worries and mistrust in medicine.

However, if patients ask their doctor to select the treatment for them, the situation becomes more difficult. For example, take the anti-cancer drug irinotecan hydrochloride. This is a drug that was developed in Japan, but was ultimately not used because it was said to cause fatalities in patients. However, it was considered to be an effective drug overseas and ultimately was reverse imported to Japan. Although the side effects of this drug are easily discernible, including diarrhea, nausea and hair loss, the effects of the treatment are not so easy to detect. No matter how good a doctor may be at communication skills, it is extremely difficult to promote understanding among patients about all aspects of medical care, no matter how long the treatment or how detailed the explanation. As medicine continues to progress it becomes ever-more complex and this brings about further gaps in understanding and perception.

To fully inform patients of the realities of medical care it is important to promote patient participation in medical associations and societies, distribute pamphlets and enhance

awareness through the medium of television. Even after such efforts have been made, however, there are still some gaps in perception and understanding. Medicine is becoming increasingly specialized and one approach is to use coordinators who can work to provide information and bridge gaps in understanding. Through these approaches alone, however, it will not be possible to eliminate cancer. The development of treatment methods and drugs that will lead to a cure are essential.

A KEY FACTOR THAT WILL BE CRUCIAL IN THE FUTURE DEVELOPMENT OF ANTI-CANCER DRUGS AND TREATMENTS IS THE ASIAN REGION ITSELF

Why Now, Why Asia?

At present, a total of 12.7 million people around the world are diagnosed with cancer each year and 7.6 million people die from cancer. A somewhat surprising fact is that almost half, or 48.1% of cancer diagnoses are in Asia. Furthermore, of all the people who die from cancer each year, 53.8% are from Asia. The population of Asia is currently rising dramatically and the proportion of the population over the age of 65 is also increasing rapidly.

A sad fact is that of the people who die from cancer in Asia, 70% are from low- to middle-income countries. According to the World Health Organization ~40% of these people who succumbed to cancer could have been saved through early detection and appropriate treatment. This is an issue that we cannot simply overlook, given that we live in the same Asian region.

Furthermore, medical care guidelines have been created based on the evidence of clinical trials. These guidelines are in common use and there is also a comprehensive database available at the National Cancer Institute of the USA, known as PDQ® (Physician Data Query). In addition, the National Comprehensive Cancer Network, a privately run body, also has guidelines in place. In contrast to the wealth of guidelines available, there is almost no data that has been gathered from evidence in Asia.

There are clear ethnic differences when we look at human metabolism and the composition of the body. This raises the question of whether it is advisable to follow guidelines that have been created based on evidence gathered overseas, predominantly in Europe and North America. There are clear ethnic differences in the response to drugs, which is influenced significantly by differences in the genome sequence. The question we face is why China, the ROK and other countries in Asia are not accumulating evidence-based data?

Unless efforts are made to implement and accumulate data from clinical research, it is impossible to say with any certainty that we are truly providing the best treatment to patients. In actual fact, in Japan clinical trials have not been implemented thoroughly and this is something that we must reflect on. We have reached a point in time where we must clarify through science what the best treatment is.

Cancer Pharmacoethnicity: Cancer and Ethnic Differences

A great deal of research, both basic and clinical, is being implemented concerning ethnic differences in response to anti-cancer drugs. There are various factors that affect such ethnic differences, including differences in the living environment, the actual differences in medical care from region to region and the interaction between various drugs. However, the single largest factor is said to be differences in genetics and genomic information. This is not an attempt to highlight ethnic differences merely for their own sake, but rather an attempt by the medical sector to provide the best treatment for the patient, by developing novel drugs and treatment methods that take into account such differences.

One of the well-known drugs that is recognized as presenting a different response depending on ethnicity is Iressa (Gefitinib). This was seen as an effective drug in Japan and its use spread rapidly, but it caused interstitial lung disease and acute lung injuries which resulted in the deaths of many patients. These symptoms had not been witnessed in clinical trials implemented in Europe and North America. In actual fact it was recognized as a highly effective drug. However, as the data from use in Europe and North America was significantly different from the data gained in Japan, the pharmaceutical companies found themselves in a quandary. It was later found to be particularly effective in treating adenocarcinoma in Asian women who had never smoked, and mutations were detected in the cells that were targeted by Iressa in these people. In other words, it became clear that differences among people and cancers have their origins in genomic information. TS1 is another example of a drug where responses vary according to ethnic differences.

Benefits of Medical Treatment in Asia

We are now in the era of molecular targeted therapies. These therapies seek out targets that are only found in cancer cells and not in normal healthy cells, and by controlling the cancer cells the therapy causes them eventually to die. Work is concentrated on identifying such molecules and creating drugs to treat them. In theory such molecular-targeted therapies will have the effect of causing only cancer cells to die and leaving healthy cells unaffected, also without the disadvantage of side effects. As the targets are clearly understood it is also predicted that targeted therapies can be tailored to meet the needs of individual patients, further boosting effectiveness. This presents the possibility that in the future it will be possible for individual patients to benefit from effective and safe treatment that is designed specifically for them.

How long will it take until drugs are able to target cancer effectively? The answer is that it will take a good deal of time. It generally takes between 10 and 15 years to discover promising seeds at the basic research stage. From then it takes between 3 and 8 years to create a usable drug. Clinical trials then require between 3 and 7 years to complete. Only 1 in 30 000 drug agents prove to be successful. However, the infrastructure and

foundation for creating anti-cancer drugs are still undeveloped in Asia, with the exception of Japan. It is said that it costs between 10 and 20 billion yen to develop a new drug in Japan and 50 billion yen in the USA. The question is whether such processes should remain in their current form and whether we should do something to address this issue?

What is the current situation in Japan with regard to drug development? In the USA approximately half of all the seeds for new drugs originate in universities or venture companies affiliated to universities. However, in Japan university-originated seeds are virtually non-existent. Although it is said that it costs between 10 and 50 billion yen to develop a single drug, the annual research budget for translational research in Japan is one-tenth of that figure. To cure cancer it is essential for the government and other research organizations to work together in close cooperation.

Efforts by the Japan Society of Clinical Oncology

Against the backdrop of the current situation in Japan, I would now like to discuss some of the efforts that are being made to create solutions. Last year I presided over the 49th Annual Meeting of the Japan Society of Clinical Oncology (JSCO) and specialists from around the world came to Japan to discuss future policies and approaches. Prior to the opening of the society's annual meeting the United Nations had decided to raise cancer on the global health agenda as a common challenge for the entire world and the JSCO expressed its support for the political declaration issued by the United Nations. As it would have little meaning merely to announce that Asia would be created as the world's third pole, deliberations have begun on how to create a new joint body for research and development and new support structures in Asia. These structures would seek to promote and support clinical research in Asia and find evidence and collect data that would help in the creation of new drugs. At the same time as developing clinical research, which is currently being advanced by ~10 000 people in Asia, efforts will be made to collect genetic information and create a data center that will help to bring information together for the purpose of developing new drugs and treatments.

The aim is also to bring together people from various research groups who are involved in research into different types of cancer and advance research together in cooperation. If pharmaceutical companies also wish to engage in activities to evaluate drugs and treatments in the Asian context, we will seek their involvement and promote joint research. Already companies have demonstrated a desire to become involved in research relating to pediatric and gynecologic cancers. The ultimate aim is to formulate medical care guidelines for all areas. The aim is to create guidelines that are based on scientific evidence and offer the best, or at least better, treatment methods for patients in Asia.

Although Japan shares a sad history with China and the Republic of Korea (ROK), as we look to the future we should aim not to compete, but to work together in close cooperation in developing cancer treatments. Japan will not be the leader of Asia forever. Partnership with Asia is now the key phrase that we should concentrate on. As an initial step I believe that we should start by considering East Asia in regional terms, rather than being defined by national borders.

DISCUSSION

Akaza: I would like to ask about the efforts to ensure even distribution of cancer treatment around the nation and whether this is a mistaken course of action. In the case of China and the ROK, there are extremely large cancer centers situated in Beijing and Seoul, respectively, where 2000–3000 patients come from around the country. These large centers offer the very latest treatments at a very high standard, and their size means that it is also possible to engage in clinical trials in one integrated location. However, in the case of Japan, the policy of ensuring even distribution around the country means that all hospitals must ensure that patients can receive the same treatment wherever they reside, resulting in energy and resources being dispersed and fragmented.

Nishiyama: With regard to that point, it could be said that Japan has adopted a more 'communist' approach than China. When the term 'even distribution' is used it gives the impression that all patients can receive the same good standard of treatment. However, there is little meaning in forcing through a policy that stipulates that hospitals in Okinawa and Akita Prefectures (on opposite sides of the country), for example, must provide identical functions and treatment. The reason for this is because the mortality rate in Okinawa is extremely low, but in Akita it is extremely high. The types of cancer that are most prevalent also differ from region to region. If the policy of even distribution aims to make every region identical and the outcomes in each region also identical, then it is a misguided policy. I believe that in the second five-year basic plan for cancer control it will be necessary to place greater emphasis on responding to such regional characteristics. It will be necessary to incorporate a new cornerstone to the policy, which allows for concentration of functions for some treatments and decentralization and dispersal for others. While a bottom-up approach is naturally important in medical treatment, it is also necessary to gain specialist input that is capable of taking into consideration future developments.

Q: I found your critique of the frontlines of medical treatment most thought provoking. There is also a history of cooperation among Asian countries, which was born more than a century ago, in an attempt to catch-up with and surpass the West.

Nishiyama: I may have spoken about partnership and cooperation in Asia, but what I am not saying is that we should compete with Western countries. Rather I think we should work together and engage in mutual cooperation, based on our respective biological backgrounds.

Q: To what degree is the bottom-up approach of 'even distribution' of treatment going to be advanced? In China there are still regions where economic development is lagging and it would be difficult to ensure 'even distribution' in such areas.

Akaza: I think that it is important to create 'bottom-up'-oriented guidelines. The question is how such guidelines could be implemented in Asia. We must highlight our own national situations and demonstrate an ideal format for medical treatment to the world, but whether that is feasible or not is another issue.

Nishiyama: We have not done anything in this direction to date. I believe that at some point in the future the situation in China will probably change very quickly. There are currently disparities that are beyond our imagination.

Q: There are many medical problems facing China at the moment, but which do you think is the most significant?

Nishiyama: It was once the case in China that there were hardly any people who had received a systematic medical education. The issue of medical care will be flagged in the future as a social issue, but in order for progress to be made it will be necessary for the medical health insurance system in China to change.

Akaza: There are no major medical associations and societies discussing such issues at the moment and so this lecture has presented a good opportunity to identify various issues, which have not been covered to date.

Conflict of interest statement

None declared.

High-dose oral tegafur-uracil maintenance therapy in patients with uterine cervical cancer

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Objective: The aim of this study was to determine the efficacy and toxicity of oral administration of tegafur-uracil (UFT) at a high dose, 600 mg/day, based on the tegafur dose, against uterine cervical cancer.

Methods: This study consisted of a retrospective analysis. From April 1986 to March 1997, 309 patients with uterine cervical cancer were registered. Oral UFT was administered to 162 patients for maintenance therapy after an initial treatment (the UFT group). The other 147 patients were not treated with UFT (the control group). The survival rate was calculated for both groups and statistically analyzedusing the log-rank test. Adverse events were compared between the UFT and control groups.

Results: In the UFT group, 103 patients (63.6%) received UFT for ≥90 days. The drug dose was 600 mg/day for 137 patients (84.6%) and 300 to 400 mg/day for the remainder. The overall survival rate was significantly higher in the UFT group than in the control group ($p<0.05$). The prognosis was particularly favorable in stage III cases, in cases of squamous cell carcinoma, and in cases that were treated concomitantly or previously by radiotherapy. The most frequent side effects were nausea/vomiting (12.2%), appetite loss (10.1%), and leukopenia/neutropenia (5.8%).

Conclusion: High-dose oral UFT maintenance treatment prolonged the disease-free survival and overall survival of patients with uterine cervical cancer, particularly of those with advanced disease.

Keywords: Follow-up studies; Maintenance chemotherapy; Survival rate; Tegafur; Uterine cervical neoplasms

INTRODUCTION

Cervical cancer is the third most common cancer in women worldwide. There are approximately 530,000 new cases and 275,000 associated deaths each year [1]. In advanced uterine cervical cancer, the addition of chemotherapy to external pelvic radiation has been proposed because systemic chemotherapy further enhances local control and improves the overall survival. The main agents are cisplatin and 5-flurouracil (5-FU), concurrent chemoradiotherapy with either weekly cisplatin or monthly cisplatin and 5-FU are recommended for patients with advanced uterine cervical cancer. Oral 5-FU is also a mainstay in the maintenance therapy for cervical cancer in most cases in Japan. Among 5-FU derivative chemotherapeutic agents, tegafur-uracil (UFT) is an oral antineoplastic drug consisting of tegafur and uracil in a fixed 1:4 molar ratio. Tegafur is an oral prodrug of 5-FU and is slowly metabolized by cytochrome P450 to 5-FU [2-4]. Uracil competitively inhibits dihydropyrimidine dehydrogenase (DPD), which results in increased and sustained plasma and tumor 5-FU concentrations. The 5-FU that results from the metabolism of tegafur is modulated by formyltetrahydrofolic acid (folic acid). More recently, studies that have compared adjuvant chemotherapy with UFT after surgery and surgery alone have been reported and clearly proved a survival benefit of adjuvant UFT treatment for lung, gastric, colorectal, and breast cancer [5-11]. In early-stage uterine cervical cancer, oral 5-FU after surgery with radiotherapy appears to be useful for patients who have some risk factors but not for those with pelvic lymph node

metastases [12]. However, the extent of impact of adjuvant treatment with oral UFT on patients with advanced cervical cancer remains unclear. Although the amount of UFT per day was high in the above-described trial, it was standardized at 300 to 400 mg/day for adjuvant therapy of advanced cervical cancer. It remains unclear whether the high dose of this oral compound will become tolerable with infrequent observation of toxic effects and result in a significant improvement in the survival rate.

This study was conducted to determine the efficacy and toxicity of adjuvant and maintenance therapy with oral administration of UFT at a high dose, 600 mg/day, based on the tegafur dose, against uterine cervical cancer.

MATERIALS AND METHODS

1. Study design

This retrospective study was planned in a total of five institutions in Kumamoto, Japan. In these five institutions, between April 1986 and March 1997, patients with advanced cervical cancer were enrolled. The patients were required to meet the following criteria: histologically confirmed primary uterine cervical carcinoma; International Federation of Gynecology and Obstetrics (1988 FIGO) stages Ib to IV; performance status of 0 to 2; adequate bone marrow, renal, and hepatic function as evidenced by a white blood cell count >3,000 cells/μL, platelet count >100,000 cells/μL, serum creatinine level <2.0 mg/dL, blood urea nitrogen (BUN) level

<30 mg/dL, serum bilirubin level <1.5 mg/dL, and serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels <2 times the normal limit; and no serious complicated illness such as renal hepatic, cardiac, or pulmonary disease. Patients also could not have previously received any biochemical modulation.

In total, 309 patients with advanced cervical cancer were allocated to either the UFT-treated group (the UFT group) or the UFT-untreated group (the control group). The study group consisted of 162 selected consecutive patients with advanced cervical cancer who were enrolled in this study at five institutions in Kumamoto between August 1992 and March 1997. The patients were treated by oral administration of UFT at a dose of 600 mg/day for maintenance therapy after an initial treatment. A group of 147 similar patients who had received the same treatment in five institutions in Kumamoto between December 1986 and March 1997 was used as an external control group. These patients were required to meet the criteria mentioned above and not treated with UFT. In the UFT and control groups, 43 patients (26.5%) and 41 patients (27.9%) received radical hysterectomy combined with pelvic lymph node dissection; 58 (35.8%) and 65 (44.2%) received radiotherapy; 26 (16.0%) and 29 (19.7%) received radiotherapy and radical surgery; and 14 (8.6%) and six (4.1%) received a combination of surgery, radiotherapy, and chemotherapy, respectively. Postoperative pelvic radiotherapy was advocated for patients with pelvic lymph node metastasis, deep stromal invasion, and

parametrial invasion. Toxicity was recorded by grade according to the National Cancer Institute Common Toxicity Criteria ver. 2.0. Monthly complete blood counts, including white blood cell, red blood cell, and platelet counts, were performed to assess myelosuppression. A complete chemistry panel, including serum creatinine, BUN, bilirubin, AST, and ALT levels, was also obtained. The UFT treatment was continued for up to 2 years until side effects became intolerable. In some cases, the dose was reduced from 600 mg/day to 300 to 400 mg/day when side effects were beyond control. Severe (grade 3/4) toxicity related to chemotherapy resulted in dose reduction.

2. Statistical analysis

Survival was estimated as the time of study entry until death as a result of any cancer. Progression-free survival was defined as the time from study entry to the initial observation of disease progression or death as a result of any cancer. The survival rate was statistically analyzed using the log-rank test. No patients were lost to follow-up in this study. Each patient was followed until death or is alive with the disease status being known. This study was approved by the Institutional Review Board of Kumamoto University (Japan).

RESULTS

The patient characteristics of the two groups are listed in **Table 1**. The median follow-up period was 52 months (range, 1 to 119 months). The patient characteristics, including background factors such as age, FIGO clinical stage, histological type, and therapeutic modality, were well balanced between the UFT and control groups. In the UFT group, 108 patients (63.5%) received UFT for ≥90 days, and the average duration was 217.2 days. The average total dose was 120.2 g (range, 1.0 to 544.0 g).

1. Response, survival, and disease-free survival

The overall survival rate was significantly higher in the UFT group (73.8%) than in the control group (60.8%; $p<0.05$) (**Table 2**, **Fig. 1A**). Next, the effect of UFT administration on survival was analyzed according to FIGO staining, histological type, and primary treatment (**Table 2**).

There was a significant difference in survival between the UFT group and the control group among the stage III patients (UFT group, 62.1%; control group, 34.9%; $p=0.012$) (**Table 2**, **Supplementary Fig. 1A**). Among the patients with squamous cell carcinoma, the overall survival was 74.1% in the UFT group and 60.7% in the control group ($p=0.062$) (**Table 2, Supplementary Fig. 1**B). The patients who were treated concomitantly or previously by radiotherapy tended to have a favorable prognosis ($p=0.068$) (**Table 2, Supplementary Fig. 1C**). However, the difference in the disease-free survival rates was not statistically significant

(**Supplementary Table 1, Fig. 1B**).

Next, we investigated the effect of long-term oral administration of UFT in the patients with cervical cancer. Among the UFT-treated patients, those who received the drug for ≥90 days had significantly higher overall and disease-free survival rates than those who received the drug for <90 days (p=0.001) (**Supplementary Tables 2, 3, Fig. 2A, B**). Long-term oral administration of UFT in patients with cervical cancer was associated with a decreased risk of recurrence and death. There was a significant difference in survival with the stage IV patients (57.1% in the patients who received the drug for ≥90 days vs. 17.1% in the patients who received the drug for <90 days) (**Supplementary Table 2**). The difference in survival was significant in the patients with squamous cell carcinoma (81.0% in the patients who received the drug for ≥90 days vs. 59.6% in the patients who received the drug for <90 days) (**Supplementary Table 2**). In the patients treated by radiotherapy, the overall survival rate was 74.9% for the long-term administration group and 44.7% for the shorter-term administration group (**Supplementary Table 2**). Squamous cell carcinoma and radiotherapy had a significant effect on disease-free rates (p<0.05) (**Supplementary Table 3**).

2. Toxicity

In total, 139 of the 162 patients enrolled in the UFT group were assessable for toxicity. Fifty-

six patients (40.3%) showed ≥1 adverse reactions; overall, high-grade toxicities were infrequently observed. The toxicities are summarized according to the worst grade per patient for all treatment courses in **Table 3**. Nausea and vomiting (17/139, 12.2%), appetite loss (14/139, 10.1%), leukopenia/neutropenia (8/139, 5.8%), elevation of serum transaminases (7/139, 5.0%), diarrhea (7/139, 5.0%), and skin/nail pigmentation (5/139, 3.6%) were the most commonly observed toxicities (**Table 3**). No patients developed grade 4 hematological or nonhematological adverse events. Overall, eight patients experienced grade 3 nonhematological adverse events in the study group. Gastrointestinal toxicity was not manageable for most patients. In particular, grade 3 hematological toxicity was observed in one patient.

DISCUSSION

This is the first report to investigate the efficacy of oral administration of a high dose (600 mg/day) of UFT in uterine cervical cancer patients. In this study, we elucidated that UFT maintenance treatment might lead a favorable prognosis in stage III cases, in cases of squamous cell carcinoma, and in cases that were treated concomitantly or previously by radiotherapy.

One particular limitation of this study warrants mention. Owing to its small sample size, this study did not have sufficiently statistical power to demonstrate the effect of UFT treatment in uterine cervical cancer patients. However, the overall survival rate was significantly higher in

the UFT group than in the control group. This difference might indicate the possibility of using UFT as a treatment option in uterine cervical cancer patients.

DPD is the initial rate-limiting enzyme in the catabolism of 5-FU and plays a critical role in regulating the availability of 5-FU for anabolism. In the treatment of advanced colorectal cancer, orally administered prodrugs of 5-FU were introduced as DPD inhibitory fluoropyrimidine drugs, including UFT. UFT can maintain a higher 5-FU plasma level for a longer period through the inhibition of 5-FU degradation [2-4,13].

Adjuvant chemotherapy can offer clinical benefits for patients receiving primary radiation therapy because 5-FU is a radiation sensitizer. Theoretically, possible mechanisms such as the inhibition of repair of radiation damage, cell synchronization, recruitment of nonproliferating cells into the cell cycle, and reduction of the hypoxic fraction are promoted. In this study, we showed that the prognosis was favorable in the UFT group that was treated concomitantly or previously by radiotherapy. Compared with continuous infusion of 5-FU and capecitabine, the combination of UFT and radiotherapy has several clinical benefits. Chemoradiotherapy that includes UFT is efficacious against solid tumors, including those in head and neck cancer [14] and non-small cell lung cancer [15]. Recently, in the treatment of resectable rectal cancer, preoperative chemoradiotherapy consisting of UFT with leucovorin plus radiotherapy was well tolerated and effective, and it represents a convenient alternative to 5-FU-based

chemoradiotherapy [16]. This study showed a correlation between the potential role of UFT and radiotherapy in uterine cervical cancer. There are some studies to evaluate the effect of adjuvant chemotherapy after chemoradiotherapy for locally advanced cervical cancer [17,18]. However, the evidence was insufficient to support the use of adjuvant chemotherapy after chemoradiotherapy in locally advanced cervical cancer. Future large trials are required to demonstrate a correlation between adjuvant chemotherapy including UFT and radiotherapy in uterine cervical cancer.

The effect of UFT has been suggested to be influenced by tumor angiogenesis and the status of angiogenesis-related factors as well as by the status of enzymes involved in 5-FU metabolism, such as TS and DPD [19-23]. In uterine cervical cancer, UFT and its metabolite gamma-butyrolactone inhibit angiogenesis induced by vascular endothelial growth factor, which causes an antitumor effect [24]. Metronomic therapy, which is continuously administered systemically at close to non-toxic doses, involves multiple mechanisms that include antiangiogenesis and antivasculogenesis. In this study, patients who received UFT administration for ≥90 days had significantly higher survival and disease-free rates than those who received the drug for <90 days. Long-term administration of UFT after primary treatment can be a key factor for improving the prognosis in uterine cervical cancer.

Our study suggested that high-dose oral UFT maintenance treatment might prolong the

disease-free survival and overall survival of patients with uterine cervical cancer. However, adverse events are likely to be more frequently observed in patients treated with high-dose UFT (600 mg/day) than in those treated with low-dose UFT (300 to 400 mg/day). Although significant myelosuppression, mucositis, or alopecia was infrequently encountered, the incidence of gastrointestinal toxicity was shown to be approximately 32% in the present study, and most of these patients were not able to continue self-administration by mouth beyond 90 days. Recently, a weekday-on/weekend-off oral UFT schedule has been frequently proposed as outpatient adjuvant chemotherapy with good tolerability.

Future studies that investigate new treatment schedules should be considered to reduce the frequency of nausea/vomiting and loss of appetite while achieving an excellent rate of compliance in self-administering high-dose UFT therapy. High-dose UFT oral administration provides a springboard from which we expect to launch better adjuvant and maintenance chemotherapy in advanced cervical cancer. Our present regimen is a potentially attractive alternative to palliative treatments for recurrent and incurable cervical cancer.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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