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COMMISSION REPORT

Toward the realization of a better aged society: Messages from gerontology and geriatrics

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1. Background: Recent medical advancements, and improvements in hygiene and food supply have led to Japan having the longest life expectancy in the world. Over the past 50 years, the percentage of the elderly population has increased fourfold from 5.7% in 1960 to 23.1% in 2010. This change has occurred at the fastest rate in the world. Compared with France, where the percentage of the elderly population has increased just twofold in the past 100 years, Japanese society is aging at an unprecedented rate. In addition, the percentage of the very elderly (aged 75 years and over), comprising more frail people, exceeded 10% of the nation's population in 2008. In such a situation, many elderly Japanese wish to spend their later years healthy, and wish to achieve great accomplishments in their lives. To achieve that, rather than considering an aging population as a negative social phenomenon, we should create a society where elderly people can enjoy a healthy, prosperous life through social participation and contribution.

Factors that hamper the elderly from leading a healthy life include various psychological and social problems occurring in older age, as well as a high incidence of diseases. Therefore, gerontology, which focuses on health promotion of the elderly by encompassing the study of social welfare, psychology, environment and social systems; and geriatrics, which focuses on health care of elderly people and carried out research, education and practices to promote health in the elderly, are becoming more important. Furthermore, along with a need for multidisciplinary care to support geriatric medicine, the development of a comprehensive education system for aged-care professionals is awaited. Thus, we should now recognize the importance of gerontology and geriatrics, and a reform of medical-care services should be made in order to cope with the coming aged society.

Population aging is a global phenomenon. The actions being taken by Japan, the world's most aged society, have been closely watched by the rest of the world. Japan's aged society has been posing not only medical, nursing and welfare problems, but also complex problems closely associated with economy, industry and culture. Therefore, to solve these

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problems, a macroscopic integration and cooperation among industries, education institutions, administration and community through an interdisciplinary approach including medical science, nursing science, nursing care, study of social welfare, social science, engineering, psychology, economics, religion and ethics should be made. Regarding the promotion of gerontology, the **"Committee for Establishing a Scientific Community for Sustainable Aged Society"** of the Science Council of Japan also prepared a proposal and this was announced on 20 April 2011.

2. Current situation and problems

(1) Promotion of social participation and contribution of elderly people

In Japan, the overall labor force rate is expected to decrease in the near future as a result of the low birth rate and high life expectancy. In contrast, many elderly people, particularly the young-old, have sufficient physical strength to fulfil their job duties and make a social contribution. For these people, a social structure where elderly people can work should be developed through re-educating the elderly and providing various job types. Promotion of social participation and contribution of the elderly is expected to cause a substantial increase in the labor force. Furthermore, it is also expected to contribute to not only the upturn of national economic activity through an increase in total consumption, but also a decrease in the number of elderly people who are likely to be in need of care. Therefore, in order for elderly people to be engaged in various social activities, strategies for developing a social structure for re-education, various employment statuses and employment opportunities should be prepared. However, as the total number of jobs is fixed, consideration should also be given to young workers.

(2) Fostering medical specialists for aging

Older people often suffer from many diseases, together with geriatric syndromes with multiple etiologies. Signs and symptoms vary according to each individual, and are often atypical; therefore, the patients visit different hospitals and receive many screening tests and prescriptions at the same time. To solve this problem, an effective screening system carried out by a primary-care doctor, and privacy-preserving medical data sharing among hospitals and clinics are needed. In a geriatric clinical setting, health-care professionals should be aware of the physical traits of older people who often develop not only dementia, but also geriatric syndromes, such as depression, falls and urinary incontinence, so that a holistic approach with consideration of nursing care is required. However, the existing Japanese medical education system is not prepared for medical professionals enabled to respond to the aforementioned requirements. Thus, the fostering of medical professionals who can provide comprehensive care – especially for the oldest-old – such as geriatric specialists and medical professionals who understand the principles of elderly care, is urgently needed.

(3) Diagnosis of elderly-specific diseases and reform of medical-care services

In Japan, the diagnostic system for elderly-specific diseases, including dementia, and reform of medical care services are markedly delayed. The current status concerning diagnosis, care and nursing should be investigated to collect academic data. In order to accumulate evidence for providing safe elderly care and nursing, the promotion of clinical research and a marked expansion of geriatric medical centers with high-level medical services are eagerly awaited.

(4) Promotion of home-based care and multidisciplinary care

To reduce the length of stay in acute hospitals, to reduce the physical burden of health-care professionals working at acute hospitals and to meet the demand of older people who prefer to remain in their own homes, further promotion of home-based care is needed. In addition, "multidisciplinary care" is increasingly needed to meet various demands in the medical care and welfare of the elderly. It is considered important to share countermeasures against the problems of disease prevention, medicine, care and welfare among health-care professionals in medicine, care and welfare, and cooperate by making the best use of health-care professionals' specialties.

3. Contents of the proposal

The subcommittee for aging, thus, provided the following proposal:

1 Development and promotion of systems that enable elderly people to participate socially and make a contribution using an interdisciplinary approach among the various areas,

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including nursing science, nursing care, study of social welfare, social science, psychology, economics, religion and ethics, as well as medical sciences;
2 Promotion of gerontology, reform and enhancement of geriatrics in undergraduate, postgraduate and lifelong education;
3 Building geriatric medical centers in each area, and accumulating large-scale evidence of geriatric diseases and geriatrics; and
4 Structural development and promotion of home-based care and multidisciplinary care.
Through implementation of the above measures, Japan is expected to function as a successful example for the rest of the world. **Geriatr Gerontol Int 2012; 12: 16–22.**

Keywords: education, elderly, geriatrics, gerontology, multidisciplinary approach.

1. Preface

Over the past 50 years, the percentage of elderly people in the population of Japan has increased fourfold from 5.7% in 1960 to 23.1% in 2010. Japanese society is aging at an unprecedented rate. According to the National Institute of Population and Social Security Research, the percentage the elderly population is estimated to continue increasing, reaching 26.0% in 2015 and further increasing rapidly. After 2020, the percentage of elderly people in the population is expected to stabilize; however, as a result of a decrease in the total population, the percentage will further increase to 40.5%, peaking in 2055. Japan will face a super-aged society, in which 40% of the population will be over 65 years-of-age. Unless appropriate countermeasures are taken, such as a rapid improvement in clinical skills and knowledge among physicians involved in geriatrics, marked advances in the prevention of lifestyle-related diseases, prevention of geriatric syndromes including dementia, and marked expansion of home-based care or local-care, we cannot avoid a situation where many frail elderly people have to live with no support. However, many issues remain; that is, a marked reduction of long-term care facilities, a reduction in length of hospital stay in acute hospitals and a delay in expanding home-based care system, and whether thanatology reflects a social change. We should also consider social issues, such as ageism, caregiver burnout, dignified death and the appropriateness of placing gastrostomy tubes in elderly patients with dementia. To provide dignified care, particularly for older people, appropriate care should be carried out in not only the terminal phase, but also during the last few years before death.

However, despite the challenge, little is known about gerontology and geriatrics in Japan, and they are not fully used in clinical settings or education. To solve this problem, a macroscopic integration and cooperation are needed, using an interdisciplinary approach involving medical science, nursing science, nursing care, study of social welfare, social science, engineering, jurisprudence, economics, psychology and ethics. Furthermore, along with the reform and enhancement of geriatrics in undergraduate and postgraduate education, fostering specialists who can practice geriatrics is needed. Also, for non-geriatricians or general practitioners who currently and prospectively provide care in clinical settings, an educational system should be prepared to deepen their understanding of geriatric medicine.

2. Current situation and measures

(1) Social contribution of the elderly and the medical economy

As a result of the low birth rate, the percentage of the total labor force (aged 20–64 years) is expected to decrease in Japan. Elderly people are usually divided into two groups based on age: 65–84 years (young-old) and 75 years and older (old-old). Although many elderly people, particularly the young-old, have sufficient physical strength to fulfil their job duties and a make social contribution though productive activity, they are not fully utilized. The promotion of social participation and the contribution of the elderly is expected to contribute to creating purpose in their lives, as well as an increase of a substantive productive population, financial stability and self-sustainability for the elderly, and an upturn of national economic activity through an increase of total consumption. Therefore, for elderly people to be engaged in various social activities, strategies for developing a social structure for re-education, volunteer activity, various employment statuses and employment opportunities should be prepared using an interdisciplinary approach involving study of social welfare, social science and economics. However, as the total number of jobs is fixed, consideration should also be given to young workers.

Life expectancy in Japan is the highest in the world. Japan also has the highest healthy life expectancy. In 2008, USA health expenditures accounted for 16% of the nation's gross domestic product (GDP), twice the Japanese rate. Compared with other countries, Japanese health expenditures as a percentage of GDP accounted for two-thirds of that of France and Germany, suggesting that we have the most cost-effective health-care

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systems. In addition, the annual cost of health care has been approximately 670 000 yen per elderly person for the past 10 years. However, the aging of the population is expected to impact on future spending growth. Sasaki compared life-long medical costs between the longevity and non-longevity groups, and found that longevity decreases medical costs and has positive economic impacts.[1] Thus, it is important to enhance preventive medicine to achieve longevity, make continuous efforts for cost-effective medicine and improve satisfaction with the health-care systems. Discussion of geriatric medicine should be made after disclosing the aforementioned facts to the public.

Problems in geriatric medicine are closely linked to social structures, including care, welfare and dwelling surrounding the health-care system. To reveal and solve problems regarding the elderly and an aged society, the promotion of gerontology using an interdisciplinary approach is increasingly needed.

Regarding employment opportunities for older workers and future directions of medicine, care and welfare, discussion should be made among specialists from various health-care specialties. The Japan Geriatrics Society and the Japan Gerontological Society, as a core organization, should expand their activities to achieve a "society where elderly people can enjoy their lives" with the cooperation of the National Center for Geriatrics and Gerontology, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, the Institute of Gerontology the University of Tokyo, and J. F. Oberlin University.

(2) The current state of geriatric medicine and its direction

Geriatric disorders have several features.

First, diseases occur as a result of a decline in organ systems associated with aging. Therefore, even if a disease is not so severe, a patient might have been developing an unexpectedly marked decline in organ systems. In addition, homeostatic function with aging, biophylaxis capacity and nutritional absorption capacity often decrease, and symptoms become chronic and refractory.

In terms of clinical symptomatology, older people often complicate many diseases together with a geriatric syndrome with multiple etiologies. Signs and symptoms vary according to each individual, and are often atypical. Response to drugs is different in elderly compared with non-elderly people.

Older people are more likely to develop multiple diseases, and visit different hospitals and receive many screening tests and prescriptions at the same time;[2] thus, total expenditures on the elderly become inevitably high, which has been said to cause financial collapse of the Japanese health insurance system. However, regarding this issue, we should focus on the medical cost required for a single disease between elderly and non-elderly people, and we should be aware that restricting the increasing financial burden on patients to receive screenings or prescriptions for each disease would be ageism for elderly people and uncontroversial. However, unnecessary duplication of the screening given at each hospital should be avoided. To achieve this, an effective screening system carried out by primary-care physicians, and privacy-preserving medical data sharing of test results and medication among hospitals and clinics are needed. Regarding medications, the Japan Geriatrics Society has prepared the "Guidelines for medical treatment and its safety in the elderly" as an outcome of the sponsored research in Japan Foundation on Aging and Health.[3] The guideline explained standard medical treatments mainly for the elderly by giving examples of low priority, such as making an easy prescription or non-evidence-based prescription to prevent deterioration of chronic disease. In either retrospective fee-for-service or a prospective payment system (fixed amount), physicians should provide the same level of prescription to each patient. To carry out effective screening for the elderly or evidence-based medical treatment, a constructive research system should be developed separately from health-care reform in terms of medical economy. The Japanese government has decided to abolish the existing medical insurance system for those aged 75 years and older; however, the following principles stated in the existing medical insurance system should be included in the next system for the elderly: (i) elderly disease prevention; (ii) comprehensive geriatric assessment; and (iii) incentives to promote discharge planning.

Older people often develop functional disorders associated with chronic disease or aging. Functional disorders not only jeopardize the independence of people and pose social disadvantage, but also lead to secondary disease. This often makes elderly people fully dependent, resulting in lower quality of life. Therefore, in the treatment of geriatric disorders, priority should be given to functional outcomes, as well as life expectancy and the prognosis of organ systems. In addition, because a psychological change associated with an environmental change often leads to a deterioration of symptoms in elderly people, treatment policy and discharge planning should be prepared with a holistic consideration of the patient using the comprehensive geriatric assessment (CGA). In geriatric medicine, it is important not only to protect organ systems, but also to maintain physical function to prevent assisted living.

To maintain independent living, a person needs to have sustained function, including daily life functions, cognitive function, emotion and sociality (family, friends, job). CGA is used to determine the aforementioned functional status both comprehensively and systematically. The results of CGA give us a clue of what kind of

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support can help maintain independent living or assisted living with minimum care for elderly people. However, CGA is not a popular tool. Therefore, we should examine ways of increasing the awareness of CGA to promote its use for the improvement of geriatric medicine.

End-of-life care for elderly patients is an extremely important issue in geriatric medicine; however, very few elderly people in Japan have made advance directives to show their wishes about their health care during the end-of-life period. In geriatrics, there are so many issues to discuss, including confirmation of patient's wishes, the need of a health-care representative, and the relationship between the patient and their physician. Therefore, we should investigate the awareness of end-of-life care for elderly patients among health-care professionals, including physicians and nurses, people involved in care, patients, and their families, to discuss future direction of care. Regarding end-of-life care in elderly people, "Attitudes toward end-of-life care in elderly patients",[4] which was announced in 2000 by the ethics committee of the Japan Geriatrics Society and is currently under revision, and a proposal prepared by the end-of-life care research group,[5] should be referred.

(3) Fostering health-care professionals involved in geriatric medicine

Despite the growth of the elderly population, physicians with special geriatric training are not expected to increase under the present system of medical education. In order to solve the problem of care for the growing elderly population, the educational system should be restructured to provide an understanding of geriatric medicine for non-geriatricians, general practitioners and physicians working at care facilities that provide care for elderly patients. This might be an effective and practical approach for fostering physicians taking care of the elderly. To provide sufficient geriatric knowledge to general practitioners and non-geriatricians, the education program should include basic geriatrics contents to retain quality of geriatric care, which would be required even for non-geriatricians. The Japan Geriatrics Society has published *Clinical Handbook for Active Aging and Geriatric Care* for physicians, which aims to provide basic knowledge of elderly-specific symptoms, assessment, treatment and care. It is expected that using this handbook for students, residents, practitioners and non-geriatricians might contribute to the expansion of geriatric medicine. In the USA, in order to deal with a shortage of geriatric specialists, medical students are required to receive a minimum geriatrics education.[6]

(4) Promotion of geriatric disease clinical research

In Japan, a system for making diagnosis and providing treatment and care for patients with elderly diseases, including dementia, has not been fully developed. In elderly care, it is important to make an accurate diagnosis and collect clinical evidence to reflect diagnosis and evidence in clinical settings. To accumulate evidence of geriatric medicine and nursing, the promotion of clinical research and a marked expansion of geriatric medical centers with high-level medical services are eagerly awaited.

Currently, there are just two geriatric medical centers in Tokyo and Nagoya. Therefore, the number of centers should be increased and should be placed in each district (Hokkaido, Tohoku, Hokuriku, Kanto, Koshinetsu, Tokai, Kinki, Chugoku, Shikoku and Kyushu). The National Center for Geriatrics and Gerontology, as a core facility, is required to examine the efficacy of geriatrics-related activities and consistency with countermeasures, supervise multicenter studies and clinical research projects, and strive to enhance geriatric medicine through the standardization of geriatric medicine and care, and preparation of medical guidelines. In this process, each center, as a platform of geriatric medicine, should accumulate clinical data, and is also required to function as a facility to educate non-geriatricians.

The Japan Geriatrics Society has been carrying out clinical research on the treatment of hyperlipemia involving the elderly aged 75 years and over. An establishment of a support system for such clinical research and an accumulation of evidence on the efficacy of nutrition and exercise are also considered important.

(5) Promotion of home-based care and multidisciplinary care

Based on the demand of older people who prefer to remain at home, and a government policy that aims to shorten the length of hospital stay and the number of beds to decrease the growing burden of health-care expenditure, the promotion of home-based care has been provided. However, the medical structure of home-based care has not been fully devised, requiring further development of a medical and nursing structure where older people can receive continuing treatment and care, including rehabilitation, within the local community, while not being too dependent on the hospital stay, or not being forced to choose home-based care. Enhancement of home-based care might contribute to reducing the burden on physicians and nurses at acute hospitals, and might also compensate for other care services, such as emergency care and obstetrics.

One of the concerns of home-based care among physicians, patients and their families is the difficulty with hospital admissions in the event of sudden illness or deterioration. To solve this problem, the National Center for Geriatrics and Gerontology has established a "Home-based care unit". Preregistration from both a general practitioner and the patient is necessary for

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admission to this unit, with the intention to continue home-based care. The patient can be admitted any time by referral of a general practitioner. The outcome of this program is eagerly awaited.

In home-based care settings, a group of professionals from diverse disciplines mutually cooperate to provide care for a patient. For such a multidisciplinary approach, it is important to choose appropriate professionals according to the condition and disease stage of the elderly patient. However, this multidisciplinary approach involves some problems. One is the legislative "gap" between health-care providers registered under the Medical and Dental Practitioners Acts and the Act on Public Health Nurses, Midwives and Nurses, and nursing care providers registered under the Long-Term Care Insurance. The other is the discrepancy in the principle between health-care and nursing-care providers. To solve these problems, it is essential to examine them along with the legislative issues, and promote home-based care, particularly at universities offering courses in geriatrics and local community hospitals where there are accumulating results of a multidisciplinary approach to caring for elderly patients, to further promote the cooperation between medical-care and social-welfare services.

3. Proposals

We make the following proposals as countermeasures against various issues in geriatrics:

(1) Development and promotion of a system that enables elderly people to participate socially and make a contribution using an interdisciplinary approach among the various areas, including nursing science, nursing care, study of social welfare, social science, engineering, psychology, economics, religion and ethics, as well as medical sciences.

Promotion of social participation and contribution of the elderly, while considering the total number of jobs and young workers, is expected to contribute to creating purpose in their lives, and reduce the growing number of older people who become frail or in need of care. It is also expected to bring about an increase in a substantial productive population, financial stability and self-sustainability for the elderly, and an upturn of the national economic activity through an increase of total consumption.

(2) Promotion of gerontology, reform, and enhancement of gerontology and geriatrics in undergraduate, postgraduate and lifelong education.

To solve problems associated with elderly people or an aged society, gerontological and geriatric research and education should be enhanced. By fostering medical professionals who understand the physical and mental traits of older adults, and those who can provide a holistic approach with consideration to organic integration with nursing care, provision of reliable care and nursing services is expected.

(3) Build geriatric medical centers in each area, and accumulate large-scale evidence of geriatric diseases and geriatrics.

For system reform of diagnosis, treatment and nursing care, evidence should be accumulated through large-scale clinical studies.

(4) Structural development and promotion of home-based care and multidisciplinary medicine and care.

Promotion of home-based care and multidisciplinary medicine and care, particularly at universities offering courses in gerontology and local community hospitals where there are accumulating results of a multidisciplinary approach to care for elderly patients, can be expected to help reduce the burden of physicians and nurses, and meet the demand of older people.

Through implementation of the aforementioned measures, Japan is expected to function as a successful model for the rest of the world.

4. Summary

The phenomenon of an aging population is often considered within a negative spectrum; however, elderly people in need of care only account for 13% of the total elderly population, and this is not being expected to further increase. We should rather focus on the fact of an increasing number of "healthy elderly individuals with rich experience and knowledge", which would not become a negative factor in the future. The restructuring of these healthy elderly resources for social development is believed to bring a permanent bright future, and it is expected that medical-care and social-welfare services will make a significant contribution within this framework. The realization of healthy longevity in society is possible; however, we should be aware that it is only possible by the integration of geriatric medicine and social welfare.

To cope with the problems that come with a rapidly aging society as the world-leading model, the development of elderly-friendly medical devices and nursing-care equipment to avoid a labor shortage is considered essential. Taking the lead in the development of medical equipment for elderly people enables us to provide other countries with aging populations with a model for success, and is also expected to contribute to the creation of new employment and an increase in export as one of the main industrial products in Japan.

The task given to the country with the longest healthy life expectancy is to try to achieve the highest level of elderly satisfaction. As a result of a community change, "roles" and "presence with respect" of the elderly have become weakened, and a medical- and nursing-care "burden" for the younger population has been casting

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a dark shadow over the society. As the baby boomer generation ages into elderly status, new roles, including a future health-care workforce and volunteer activities, and community satisfaction should be rebuilt. Gerontology and geriatrics ought to take the lead in showing a practical approach to the industry and the administration to create new images of the elderly.

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Disclosure statement

The authors declare no conflict of interest.

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Original Article

Comparative study of cisplatin and epirubicin in transcatheter arterial chemoembolization for hepatocellular carcinoma

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Aim: Transcatheter arterial chemoembolization (TACE) is an established treatment for unresectable hepatocellular carcinoma (HCC). However, it is unclear which chemotherapeutic agent should be selected for TACE. The aim of this study was to compare the efficacy of cisplatin (CDDP) with that of epirubicin (EPI) in TACE for patients with unresectable or relapsed HCC.

Methods: We performed a historical cohort study involving 131 patients treated with a first TACE, defined as either an initial treatment for previously untreated HCC or a first treatment for relapsed HCC after curative resections or ablations. Efficacy was estimated as the response rate (RR) and it was adjusted for the confounding factors that were defined in this study.

Results: The RR were 62.5% (20/32) for the first TACE with CDDP and 51.5% (51/99) for that with EPI. In the adjusted analysis for a history of hepatectomy, percutaneous treatment combined with TACE and tumor factors, the odds ratio was 1.72 (95% confidence interval [CI] = 0.70–4.48). However, a test for interaction between the number of tumors and the chemotherapeutic agent was statistically significant ($P = 0.016$). In multiple HCC, the RR were 66.7% (10/17) for CDDP and 39.6% (30/46) for EPI. The odds ratio was 4.11 (95% CI = 1.14–17.2).

Conclusion: CDDP may be more effective than EPI in TACE for multiple HCC. A randomized controlled study is needed to clarify the efficacy of CDDP in TACE in patients with multiple HCC.

Key words: cisplatin, epirubicin, hepatocellular carcinoma, transcatheter arterial chemoembolization, treatment

INTRODUCTION

EVERY YEAR, AT least 626 000 people die of hepatocellular carcinoma (HCC).[1] Even if a curative resection is performed, 80% of patients develop an intrahepatic recurrence because of either intrahepatic metastases from the primary tumor or multicentric carcinogenesis.[2] Therefore, a therapeutic strategy against advanced or relapsed tumors is vital for improving the prognosis of HCC.

Transcatheter arterial chemoembolization (TACE) provides a survival benefit in patients with unresectable or relapsed HCC.[3–6] Chemotherapeutic agents currently used for TACE are doxorubicin, epirubicin (EPI), mitomycin and cisplatin (CDDP).[7] Furthermore, doxorubicin-loaded drug-eluting beads (DEB) have been recently used for TACE.[8,9] However, ischemia resulting from embolization may be the main factor inducing a reduction in tumor size after TACE.[7] Therefore, it is unclear whether the selection of chemotherapeutic agents influences the efficacy of embolization. The most appropriate chemotherapeutic agent for TACE has not been established.[10]

The aim of this study was to compare the efficacy of CDDP and EPI in TACE for patients with unresectable or relapsed HCC. We focused the number of tumors and the efficacy was adjusted for the confounding factors defined in this study.

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METHODS

THE KYOTO UNIVERSITY Graduate School and Faculty of Medicine Ethics Committee approved this study in accordance with ethics guidelines for epidemiological studies in Japan (E-692). All patients gave informed consent for TACE.

Study design and eligibility criteria

We performed a historical cohort study to compare the efficacy of the first TACE with CDDP (CDDP-TACE) with that of the first TACE with EPI (EPI-TACE). Between 1 January 2003 and 31 December 2008, patients at Kyoto University Hospital who were diagnosed with HCC and treated with TACE were selected for this study. All patients were followed until 31 March 2009. In this study, we defined first TACE as TACE either for previously untreated HCC or for HCC that relapsed after curative hepatectomy, radiofrequency ablation (RFA) or percutaneous ethanol injection therapy (PEIT). The eligibility criteria of this study were the first TACE with or without simultaneous RFA or PEIT as a supplementary treatment. Patients under treatment for another type of cancer and/or who were diagnosed with extrahepatic metastasis of HCC were excluded. Patients who had been treated with hepatic arterial infusion chemotherapy and/or transcatheter arterial injection were also excluded.

Treatment

Using Seldinger's method, either powdered CDDP suspended in lipiodol or EPI dissolved in a contrast medium suspended in lipiodol was injected as selectively as possible into the hepatic segmental artery supplying the HCC. We had not selected a chemotherapeutic agent at random. EPI is commonly selected in clinical practices. CDDP was selected mainly because of a clinical research trial for the safety of TACE with CDDP.[11] Dosage of a chemotherapeutic agent was decided by the tumor load of HCC and it was administrated as 4 mg EPI and 10–20 mg CDDP per 1 cm of tumor diameter. The feeding arteries were embolized using a gelatin sponge.[12] A repeat TACE was not scheduled without a relapse of the tumors or insufficient treatment.

Assessment of efficacy

The efficacy of TACE was assessed by dynamic computed tomography (CT) or magnetic resonance imaging (MRI) scan within 3 months of first TACE. At least two medical doctors specializing in surgery or radiology at Kyoto University Hospital evaluated all CT or MRI scans.

Response to treatment was defined according to the European Association for the Study of the Liver (EASL) criteria.[13] The efficacy of TACE was evaluated as the response rate (RR), that is, the proportion of patients showing a complete or partial response.

Overall survival (OS) was defined as the interval between the day of the first TACE and the day of death from any cause. Patients who failed to undergo follow-up procedures were excluded on the last day when they were confirmed to be alive.

Confounding factors

Extraneous factors that are related to both the intervention and the outcome may distort the relationship in a study.[14] These extraneous factors are known as confounding factors.[14]

In HCC, prognostic factors such as the number of tumors, tumor diameter and vascular invasion have been established and some staging systems are constructed based on the prognostic factors, tumor markers and Child–Pugh classification.[15,16] TACE is selected according to algorithms that are decided by either prognostic factors or the staging system.[15] The selection criteria of TACE are practically changed by some factors such as previous hepatectomy, location of recurrent HCC and vascular invasion.

We defined the number of tumors, tumor diameter, vascular invasion, α-fetoprotein (AFP), prothrombin induced by vitamin K absence or antagonist-II (PIVKA-II), history of hepatectomy and RFA or PEIT combined with TACE as confounding factors.

We included RFA or PEIT combined with TACE in the eligibility criteria because it can be practically done after TACE whichever chemotherapeutic agent is selected. Furthermore, we defined it as a confounding factor. However, it would affect the RR directly. Therefore, we additionally estimated the RR in the patients without RFA or PEIT combined with TACE.

Statistical analyses

JMP for Windows software ver. 8.0 was used for all statistical analyses. We used the χ^2-test (without Yates' correction) for categorical comparisons of patient characteristics and confounding factors. Student's *t*-test was used to detect differences in the means of continuous variables. Probability of survival was calculated by the Kaplan–Meier method and examined using the log-rank test. A *P*-value of less than 0.05 indicated statistical significance. All tests were two-tailed.

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We calculated the relative risk for the RR and the associated 95% confidence interval (CI). In unadjusted analyses, we included only the chemotherapeutic agent as a covariate when calculating the odds ratio of the RR and the associated 95% CI within a logistic regression model. In adjusted analyses, we included all of the confounding factors in addition to the chemotherapeutic agent as covariates to calculate the odds ratio.

To test the interaction between the number of tumors and the chemotherapeutic agent, the product term that was constructed by the number of tumors and the chemotherapeutic agent was added as a covariate into the logistic regression model. After the test for interaction, we stratified patients by the number of tumors and estimated the odds ratio of the RR in both the unadjusted and adjusted analyses.

RESULTS

Patients

AMONG 940 CONSECUTIVE patients who were treated with TACE for HCC, 135 met the eligibility criteria. Four patients treated with EPI-TACE did not undergo any radiological imaging after the first TACE. Thus, 131 patients were enrolled in this study.

In total, 99 patients were treated with EPI-TACE and 32 patients were treated with CDDP-TACE. Median observation periods were 19 and 25 months for patients treated with CDDP-TACE and EPI-TACE, respectively. Patient characteristics are shown in Table 1. There were no statistical differences between the groups.

Relationship between RR and OS

We compared OS between responders and non-responders to the first TACE to examine the relationship between the RR and OS. The OS of responders to the first TACE was significantly longer than that of non-responders ($P = 0.0025$).

Response rates of patients treated with CDDP-TACE or EPI-TACE

The RR were 62.5% (20/32) and 51.5% (51/99) for patients treated with CDDP-TACE and EPI-TACE, respectively. In the unadjusted analysis, the relative risk and the odds ratio of CDDP-TACE versus EPI-TACE were 1.21 (95% CI = 0.87–1.69) and 1.56 (95% CI = 0.70–3.63), respectively. In the adjusted analysis, the odds ratio was 1.72 (95% CI = 0.70–4.48).

Test for interaction and stratification of patients by number of tumors

The test for interaction between the number of tumors and the chemotherapeutic agent was statistically significant in the adjusted analysis ($P = 0.016$). We stratified patients by the number of tumors and compared the efficacy. Both single HCC and multiple HCC groups were adjusted for the confounding factors (Table 2).

The RR of patients with a single tumor were 58.8% (10/17) and 65.2% (30/46) for CDDP-TACE and EPI-TACE, respectively. In the unadjusted analysis, the relative risk and the odds ratio of CDDP-TACE versus EPI-TACE for a single tumor were 0.90 (95% CI = 0.57–1.41) and 0.76 (95% CI = 0.024–2.45), respectively. In the adjusted analysis, the odds ratio for a single tumor was 0.43 (95% CI = 0.094–1.94).

On the other hand, the RR of patients with multiple tumors were 66.7% (10/15) and 39.6% (21/53) for CDDP-TACE and EPI-TACE, respectively. In the unadjusted analysis, the relative risk and the odds ratio of CDDP-TACE versus EPI-TACE for multiple tumors were 1.68 (95% CI = 1.03–2.74) and 3.05 (95% CI = 0.94–11.0), respectively. The odds ratio for multiple tumors was 4.11 (95% CI = 1.14–17.2) in the adjusted analysis (Table 3).

When the patients receiving the RFA or PEIT combined with TACE were excluded, RR of patients with a single tumor were 75.0% (9/12) and 65.3% (21/32) for CDDP-TACE and EPI-TACE and the RR of patients with multiple tumors were 71.4% (10/14) and 37.0% (17/46) for CDDP-TACE and EPI-TACE, respectively. For the patients with multiple tumors, the relative risk and the odds ratio were 1.93 (95% CI = 1.17–3.19) and 4.53 (95% CI = 1.22–16.8). CDDP-TACE also showed higher RR than EPI-TACE in this analysis.

DISCUSSION

THERE HAVE BEEN few randomized controlled studies comparing the effectiveness of different chemotherapeutic agents in TACE.[10] Four observational studies compared the efficacies of CDDP and doxorubicin in TACE. Three of these studies reported that TACE with CDDP showed a better survival rate than TACE with doxorubicin.[12,17,18] The fourth study did not find a significant difference between the two agents.[19] The present study could not demonstrate a clear difference in efficacy between CDDP-TACE and EPI-TACE. Nevertheless, the test for interaction between the number of tumors and the chemotherapeutic agent was statistically

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Table 1 Characteristics of patients treated with EPI-TACE or CDDP-TACE

Patient characteristics	EPI-TACE ($n = 99$)	CDDP-TACE ($n = 32$)	*P*-value
Age			
Mean ± SD	68.4 ± 7.9	70.0 ± 5.3	0.29
Sex (%)			
Male	79 (80%)	25 (78%)	
Female	20 (20%)	7 (22%)	0.84
Hepatitis virus (%)			
HBsAg positive	17 (17%)	3 (9%)	
HCVAb positive	58 (59%)	22 (69%)	
Both positive	2 (2%)	1 (3%)	
Both negative	22 (22%)	6 (19%)	0.65
Child–Pugh classification (%)			
A	77 (78%)	27 (84%)	
B	22 (22%)	5 (16%)	0.42
PLT (%)			
$<10^4/\mu L$	33 (33%)	14 (44%)	
$\geq 10^4/\mu L$	66 (67%)	18 (56%)	0.29
Number of tumors (%)			
Single	46 (46%)	17 (53%)	
Multiple	53 (54%)	15 (47%)	0.48
Tumor diameter (%)			
<2 cm	66 (67%)	18 (56%)	
≥2 cm	33 (33%)	14 (44%)	0.29
Vascular invasion (%)			
Present	2 (2%)	2 (6%)	
Absent	97 (98%)	30 (94%)	0.23
AFP (%)			
<400 ng/mL	80 (82%)	27 (84%)	
≥400 ng/mL	18 (18%)	5 (16%)	0.72
PIVKA-II (%)			
<40 mAU/mL	47 (48%)	15 (48%)	
≥40 mAU/mL	52 (52%)	16 (52%)	0.93
History of hepatectomy (%)			
Present	68 (69%)	23 (71%)	
Absent	31 (31%)	9 (29%)	0.73
RFA or PEIT combined with TACE (%)			
Present	21 (21%)	6 (19%)	
Absent	78 (79%)	26 (81%)	0.76

AFP was not evaluated for one patient treated with EPI-TACE. PIVKA-II was not evaluated for another patient treated with CDDP-TACE. AFP, α-fetoprotein; CDDP, cisplatin; EPI, epirubicin; RFA, radiofrequency ablation; PIVKA-II, prothrombin induced by vitamin K absence or antagonist-II; PEIT, percutaneous ethanol injection therapy; TACE, transcatheter arterial chemoembolization; CDDP-TACE, the first TACE with CDDP; EPI-TACE, the first TACE with EPI; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibodies; PLT, platelets; SD, standard deviation.

significant. Therefore, we stratified patients by the number of tumors to compare the efficacy between CDDP-TACE and EPI-TACE.[20]

Previous studies reported that RR after TACE are similar to those obtained by mechanical occlusion alone.[10] Ischemia resulting from embolization may be the main factor inducing reduction in tumor size after TACE.[7] However, in this study, a difference in efficacy between the chemotherapeutic agents was observed in multiple HCC. Therefore, CDDP may have an additive antitumoral effect in multiple HCC. A previous study reported that CDDP appeared to yield the best RR when the antitumor efficacies of different anticancer agents were compared after intra-arterial infusion.[21] In TACE,

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Table 2 Confounding factors of patients treated with EPI-TACE or CDDP-TACE after stratification of the number of tumors

Confounding factors	Single tumor			Multiple tumors		
	EPI-TACE ($n = 46$)	CDDP-TACE ($n = 17$)	*P*-value	EPI-TACE ($n = 53$)	CDDP-TACE ($n = 15$)	*P*-value
Tumor diameter (%)						
<2 cm	32 (70%)	13 (76%)		34 (64%)	5 (33%)	
≥2 cm	14 (30%)	4 (24%)	0.59	19 (36%)	10 (64%)	0.033
Vascular invasion (%)						
Present	0 (0%)	1 (6%)		2 (4%)	1 (7%)	
Absent	46 (100%)	16 (94%)	0.10	51 (96%)	14 (93%)	0.63
AFP (%)						
<400 ng/mL	37 (80%)	15 (88%)		43 (83%)	12 (80%)	
≥400 ng/mL	9 (20%)	2 (12%)	0.47	9 (17%)	3 (20%)	0.81
PIVKA-II (%)						
<40 mAU/mL	23 (50%)	10 (63%)		24 (44%)	5 (33%)	
≥40 mAU/mL	23 (50%)	6 (37%)	0.39	29 (56%)	10 (67%)	0.41
History of hepatectomy (%)						
Present	30 (65%)	14 (82%)		38 (72%)	9 (60%)	
Absent	16 (35%)	3 (18%)	0.19	15 (28%)	6 (40%)	0.39
RFA or PEIT combined with TACE (%)						
Present	14 (30%)	5 (29%)		7 (13%)	1 (7%)	
Absent	32 (70%)	12 (71%)	0.47	46 (87%)	14 (93%)	0.49

AFP was not evaluated for one patient with multiple tumors treated with EPI-TACE. PIVKA-II was not evaluated for another patient with single tumors treated with CDDP-TACE.

AFP, α-fetoprotein; CDDP, cisplatin; EPI, epirubicin; RFA, radiofrequency ablation; PIVKA-II, prothrombin induced by vitamin K absence or antagonist-II; PEIT, percutaneous ethanol injection therapy; TACE, transcatheter arterial chemoembolization; CDDP-TACE, the first TACE with CDDP; EPI-TACE, the first TACE with EPI.

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Table 3 Risk ratio and odds ratio after stratification of the number of tumors

	Relative risk	95% CI	Odds ratio	95% CI
Single tumor				
Unadjusted	0.90	0.57–1.41	0.76	0.024–2.45
Adjusted			0.43	0.094–1.94
Multiple tumors				
Unadjusted	1.68	1.03–2.74	3.05	0.94–11.0
Adjusted			4.11	1.14–17.2

The unadjusted odds ratio of CDDP-TACE vs EPI-TACE is assessed within a logistic regression model that includes only the chemotherapeutic agent. The adjusted odds ratio is assessed within the logistic regression model that includes the chemotherapeutic agent and the confounding factors. CDDP-TACE, the first transcatheter arterial chemoembolization with cisplatin; CI, confidence interval; EPI-TACE, the first transcatheter arterial chemoembolization with epirubicin.

CDDP is gradually released into the systemic circulation.[22] CDDP might have effects on multiple HCC that include intrahepatic metastasis and tumors that are proliferating outside the capsule. Furthermore, CDDP is reported to be highly sensitive to some types of HCC.[23] The number of tumors may also be considered as a predictive factor for the sensitivity of CDDP.

On the other hand, CDDP-TACE may be less effective than EPI-TACE for single HCC. However, we practically use EPI in TACE for both simple and multiple HCC. Consequently, we are currently conducting a randomized controlled study to clarify the efficacies between CDDP and EPI in multiple HCC.

TACE is repeatedly used to treat relapses of HCC, as well as various therapeutic and prognostic factors influence the OS. On the other hand, the RR has been identified as an independent predictor of survival in HCC patients.[3,6,10] In this study, the OS in responders to the first TACE was significantly better than that in non-responders. Therefore, in this study, RR is considered to be more useful than OS for the evaluation of the efficacy of the chemotherapeutic agent in TACE. In this study, the 2-year survival rates were 84.5% for CDDP-TACE and 75.5% for EPI-TACE. For multiple HCC, the 2-year survival rates of patients were 77.0% for CDDP-TACE and 74.5% for EPI-TACE. TACE were repeated several times after the first TACE in most patients. Furthermore, repeated TACE with different chemotherapeutic agents were performed in 23 of 32 patients with CDDP-TACE and 43 of 99 patients with EPI-TACE.

Caution should be exercised in the use of CDDP, because CDDP has disadvantages such as the risk of nausea, vomiting, fever and thrombocytopenia.[11] Drug delivery systems (such as doxorubicin-loaded DEB) that promote long-lasting intratumoral retention of the drug may be means of decreasing systemic side-effects while increasing local chemotherapeutic effects.[8,9] The RR reported in a study investigating doxorubicin-loaded DEB was 66.6%,[8] which is similar to the RR in this study. Therefore, further studies will be needed to compare the contributions of drug delivery systems and/or chemotherapeutic agents to the efficacies of TACE.

In conclusion, the interaction between the number of tumors and the chemotherapeutic agent was observed in this study to compare the efficacy between CDDP-TACE and EPI-TACE. CDDP might be more effective than EPI in TACE for multiple HCC. A randomized controlled trial is needed to clarify the efficacy of CDDP, especially in patients with multiple HCC.

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Multicenter Phase II Study of Gemcitabine and S-1 Combination Therapy (GS Therapy) in Patients With Metastatic Pancreatic Cancer†

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Objective: The aim of this multicenter Phase II study was to assess the efficacy and toxicity of gemcitabine and S-1 combination therapy for metastatic pancreatic cancer.
Methods: Chemotherapy-naïve patients with histologically or cytologically proven metastatic pancreatic adenocarcinoma were eligible for this study. Gemcitabine was administered at a dose of 1000 mg/m^2 over 30 min on days 1 and 8, and oral S-1 at a dose of 40 mg/m^2 twice daily from days 1 to 14, repeated every 3 weeks.
Results: A total of 55 patients were included and the efficacy and toxicity were analyzed in 54 patients who received at least one dose of gemcitabine and S-1 combination therapy. Although no complete response was seen, a partial response was achieved in 24 patients, resulting in an overall response rate of 44.4% (95% confidence interval: 30.9–58.6%). The median progression-free survival was 5.9 months (95% confidence interval: 4.1–6.9 months) and the median overall survival was 10.1 months (95% confidence interval: 8.5–10.8 months) with a 1-year survival rate of 33.0%. The major Grade 3–4 toxicities were neutropenia (80%), leucopenia (59%), thrombocytopenia (22%), anorexia (17%) and rash (7%). Hematological toxicity was mostly transient and there was only one episode of febrile neutropenia ≥Grade 3.
Conclusions: Gemcitabine and S-1 combination therapy produced a high response rate with good survival in patients with metastatic pancreatic cancer. A randomized Phase III study to confirm the efficacy of gemcitabine and S-1 combination therapy is ongoing.

Key words: pancreatic cancer – Phase II – chemotherapy – gemcitabine – S-1

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INTRODUCTION

Pancreatic cancer is a highly malignant disease and the fifth most common cause of cancer death in Japan. Approximately 80% of patients are ineligible for surgery at diagnosis and more than half of patients have metastatic disease.

Gemcitabine has been the standard chemotherapeutic agent for metastatic pancreatic cancer on the basis of a Phase III study showing clinical and survival benefits over 5-fluorouracil (5-FU) (1). However, the efficacy of gemcitabine monotherapy for advanced pancreatic cancer is limited; most clinical trials have shown response rates of around 10% with a median overall survival of 6–7 months (2–5). Therefore, numerous studies have attempted to increase the efficacy of chemotherapy, but almost all the regimens evaluated in Phase III studies have failed to show survival benefits over gemcitabine. To date, only two randomized trials, gemcitabine plus erlotinib and combination therapy of 5-FU/leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) have shown significant prolongation of overall survival (6,7). However, the reported difference in median survival between the gemcitabine plus erlotinib group and the gemcitabine-only group was small (6.24 versus 5.91 months). The results of the FOLFIRINOX trial are more impressive than those of gemcitabine plus erlotinib because FOLFIRINOX led to a median survival of 11.1 months compared with 6.8 months in the gemcitabine group. However, the FOLFIRINOX regimen was quite toxic (e.g. 5.4% of patients had Grade 3 or 4 febrile neutropenia), and a survival benefit was shown only among a highly select population with a good performance status, an age of 75 years or younger and normal or nearly normal bilirubin levels (8).

S-1, an oral fluoropyrimidine derivative, is now widely used for a variety of malignancies such as gastric cancer (9,10). In Phase II studies of S-1 for metastatic pancreatic cancer, response rates of 21.1–37.5% and median overall survival of 5.6–9.2 months were reported (11,12). Preclinical studies have demonstrated a synergy between gemcitabine and 5-FU in tumor cell lines, including pancreatic cancer cells (13). On the basis of these findings, we decided to investigate combination therapy with gemcitabine and S-1 therapy (GS therapy) for pancreatic cancer. We initially conducted a Phase I study of GS therapy in patients with advanced pancreatic cancer (14). In that study, gemcitabine was administered as a 30-min intravenous infusion on days 1 and 8 along with oral S-1 twice daily from day 1 through day 14, concluding that a gemcitabine dose of 1000 mg/m^2 and an S-1 dose of 40 mg/m^2 twice daily was recommended in future studies. Since GS therapy showed promising activity, with a 33% response rate and a median survival of 7.6 months, the present multicenter Phase II study was conducted in patients with metastatic pancreatic cancer to evaluate the efficacy and toxicity profile of GS therapy.

PATIENTS AND METHODS

Patient Selection

Patients were included if they fulfilled the following eligibility criteria: histologically or cytologically confirmed adenocarcinoma or adenosquamous carcinoma of the pancreas; at least one measurable metastatic lesion; no history of prior chemotherapy or radiotherapy for pancreatic cancer; age 20–74 years; Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate organ functions (leucocyte count, 4000–12 000/mm^3; neutrophil count, $\geq$2000/mm^3; platelet count, $\geq$100 000/mm^3; hemoglobin level, $\geq$9.0 g/dl; serum creatinine level, $\leq$1.5 mg/dl; serum AST and ALT levels, $\leq$150 U/l and serum total bilirubin level, $\leq$2.0 mg/dl or $\leq$3.0 mg/dl if biliary drainage was present).

The exclusion criteria were as follows: symptomatic pulmonary fibrosis or interstitial pneumonia; watery diarrhea; active infection; marked pleural effusion or ascites; central nervous system metastasis; active concomitant malignancy; severe mental disorder; serious complications such as active gastrointestinal ulcer or severe diabetes mellitus and pregnancy or lactation. The study was approved by the institutional review board of each participating center, and was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Research (the Ministry of Health, Labour and Welfare, Japan). Written informed consent was obtained from all patients. This study is registered in the UMIN Clinical Trials Registry with the identifier C000000173.

Treatment

This study was an open-label, multicenter, single-arm Phase II study. The dose schedule of gemcitabine and S-1 was planned based on the results of the previous Phase I study (14): gemcitabine at a dose of 1000 mg/m^2 was administered as a 30-min intravenous infusion weekly for 2 weeks followed by 1 week of rest. Oral S-1 was administered at a dose of 40 mg/m^2 twice daily (80 mg/day for body surface area (BSA) $<$1.25 m^2, 100 mg/day for 1.25 $\leq$ BSA $<$ 1.50 m^2 and 120 mg/day for BSA $\geq$1.50 m^2) from days 1 to 14 followed by a 1 week rest period. The treatment was repeated every 3 weeks until disease progression, unacceptable toxicity or patient refusal.

Prophylactic administration of antiemetic agents such as dexamethasone and/or a 5-HT3 receptor antagonist was allowed at the investigator's discretion. If patients showed a leucocyte count of $<$2000/mm^3 or $>$12 000/mm^3, or a platelet count of $<$70 000/mm^3 during the cycle, administration of both gemcitabine and S-1 was suspended. If patients showed a leucocyte count of $<$3000/mm^3 or $>$12 000/mm^3, platelet count of $<$100 000/mm^3, total bilirubin $>$3.0 mg/dl, AST and ALT levels $>$150 U/l, or a creatinine level $>$1.5 mg/dl, initiation of the next cycle was postponed until recovery. When patients experienced (i) Grade 4 leucopenia or neutropenia, (ii) febrile

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neutropenia or infection with Grade 3 leucopenia or neutropenia, (iii) Grade 4 thrombocytopenia or Grade 3 thrombocytopenia requiring transfusion or (iv) ≥Grade 3 non-hematological toxicity excluding anorexia, nausea, vomiting, constipation, fatigue and hyperglycemia, the dose of gemcitabine was reduced to 800 mg/m^2 and the dose of S-1 was reduced by 20 mg/day in the subsequent cycle. The protocol treatment was discontinued if the patients required more than two dose reductions or if the subsequent cycle could not be initiated within 28 days after the final day of the anti-cancer drug administration in the previous cycle.

Evaluation

All the eligible patients who received at least one dose of GS therapy were included in the response and toxicity evaluations. Physical examination, complete blood cell counts and biochemistry tests were assessed at least on days 1 and 8 in each cycle during chemotherapy. Tumor marker carbohydrate antigen (CA) 19-9 was measured every 4–6 weeks. Objective tumor response was evaluated every 4–6 weeks by computed tomography or magnetic resonance imaging according to the Response Evaluation Criteria In Solid Tumors version 1.0. For the purpose of confirmation of objective response, an interval of at least 4 weeks was required for complete response (CR), partial response (PR) and stable disease (SD) in this study. The response duration was defined as the interval from the first documentation of response (PR or CR) to the first documentation of tumor progression. Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Progression-free survival (PFS) was calculated from the date of the initiation of treatment until documented disease progression or death due to any cause (whichever occurred first); overall survival was calculated from the date of treatment initiation to the date of death or censored at the last follow-up. An external review committee confirmed objective responses and adverse events.

Statistical analysis

The primary endpoint was the response rate (CR and PR) of GS therapy. Forty-nine patients were required based on the assumption of an expected response rate of 25% and the threshold rate of 10%, with α-error of 2.5% (one-sided) and β-error of 20%. In consideration of ineligible patients or those who dropped out, it was planned that 55 patients would be included in this study. We calculated the response rate with 95% confidence interval (CI) in the patients who met eligibility criteria and received at least one GS therapy. The progression-free and overall survival periods were estimated by the Kaplan–Meier method.

RESULTS

Patients

Fifty-five patients were enrolled from 10 institutions between October 2004 and July 2005. Of these 55 patients, one patient was excluded from analysis because he left the study before administration of GS therapy due to an allergic skin reaction caused by insulin. All of the remaining 54 patients received at least one dose of GS therapy and were included in the evaluation of response and toxicity. Patient characteristics of the 54 patients are listed in Table 1. All patients had metastatic disease and no patient received any prior therapies except surgery for pancreatic cancer. Six patients underwent percutaneous transhepatic or endoscopic biliary drainage for obstructive jaundice prior to the study enrollment.

Treatments

The final data were fixed on 31 March 2007. A total of 425 therapy cycles were administered to the 54 patients,

Table 1. Patient characteristics ($n = 54$)

Characteristics		Number of patients (%)
Median age, years (range)	62 (32–74)	
Sex		
Women		24 (44)
Men		30 (56)
ECOG performance status		
0		38 (70)
1		16 (30)
Body surface area		
Median (range), m^2	1.59 (1.18–1.83)	
History of surgical resection		9 (17)
Metastatic disease		54 (100)
Sites of metastasis		
Liver		50 (93)
Distant lymph nodes		11 (20)
Peritoneum		3 (6)
Lung		2 (4)
Other		2 (4)
Histology		
Adenocarcinoma		53 (98)
Adenosquamous carcinoma		1 (2)
Differentiation		
Well		2 (4)
Moderate		28 (52)
Poor		13 (24)
Unknown		11 (20)

ECOG, Eastern Cooperative Oncology Group.

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Table 2. Efficacy results

		Number of patients (%)
Tumor response ($n = 54$)		
Complete response		0 (0)
Partial response		24 (44.4)
Stable disease		26 (48.1)
Progressive disease		2 (3.7)
Cannot be evaluated		2 (3.7)
Response rate (95% CI), %	44.4 (30.9–58.6)	
Tumor control rate (95% CI), %	92.6	
CA 19-9 response ($n = 41$)		
Decreased (≥50%)		35 (85.4)
Decreased (<50%)		3 (7.3)
Increased		3 (7.3)
Progression-free survival ($n = 54$)		
Median (95% CI), months	5.9 (4.1–6.9)	
Overall survival ($n = 54$)		
Median (95% CI), months	10.1 (8.5–10.8)	
1-year survival rate, %	33	

CA 19-9, carbohydrate antigen 19-9.

with a median of 7 cycles each (range, 1–24). GS therapy could generally be administered on an outpatient basis. The gemcitabine on day 8 was administered in 367 (86.4%) of 425 cycles. Dose reduction was required in 30 patients (55.6%), mainly due to leucopenia, neutropenia, rash or gastrointestinal toxicities. At the time of analysis, protocol treatment was discontinued in 52 patients because of disease progression ($n = 30$) or adverse events ($n = 22$). The reasons for discontinuation due to adverse events were the second episode of Grade 4 neutropenia after one dose reduction (11), prolonged myelosuppression (3), anorexia or nausea (4), rash (2), cerebral infarction (1) and cholangitis (1). After discontinuation of GS therapy, 30 patients received gemcitabine-based chemotherapy, 6 patients received other anticancer drugs including irinotecan and the remaining 18 patients received only supportive care.

Efficacy

The efficacy results are shown in Table 2. Of the 54 patients, 2 patients could not be assessed for response since they withdrew their consent due to toxicity before the first response evaluation. Although no CR was observed, a PR was achieved in 24 of 54 patients, resulting in an overall response rate of 44.4% (95% CI: 30.9–58.6%). The median response duration was 5.3 months (range, 2.4–15.6 months). SD was noted in 26 patients (48.1%) and progressive disease (PD) in 2 patients (3.7%). The serum CA 19-9 level was reduced to less than half from baseline values in 35 (85.4%) of the 41 patients whose pretreatment levels were >100 U/ml. The median PFS was 5.9 months (95% CI: 4.1–6.9 months) with a median overall survival of 10.1 months (95% CI: 8.5–10.8 months) and a 1-year survival rate of 33.0% (Fig. 1).

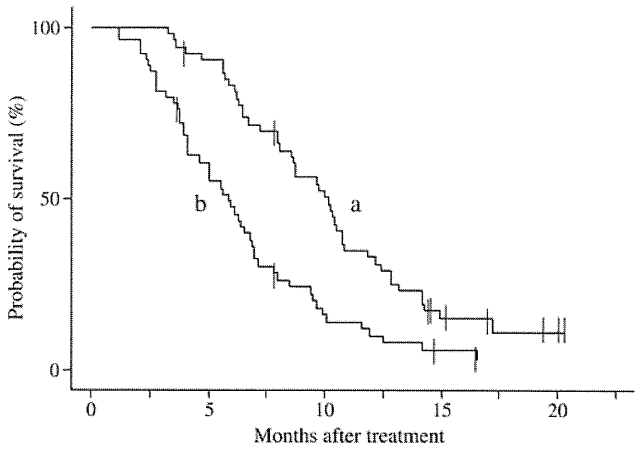

Figure 1. Overall survival curve (a) and progression-free survival (b) for 54 patients.

Toxicity

The major toxicities observed in the 54 patients are listed in Table 3. The most common toxicity was myelosuppression. Grade 3–4 neutropenia and thrombocytopenia occurred in 80 and 22% of the patients, respectively. The neutrophil and platelet count nadirs typically were observed on day 15. Although most of these hematologic toxicities were transient and recovered without serious events, one patient developed Grade 3 febrile neutropenia. No other unexpected severe toxicities were observed during the study and there were no treatment-related deaths. Although gastrointestinal toxicities and skin rash were frequently observed, most of these were manageable with appropriate medical treatment. There were no cumulative toxicities.

DISCUSSION

The major toxicity of GS therapy is myelosuppression, especially neutropenia. Although the incidences of Grade 3–4 neutropenia and thrombocytopenia observed in the current study were high (Table 3), most of these episodes were transient. There was only one episode of neutropenic fever without treatment-related death. Therefore, most patients could be treated on an outpatient basis without receiving granulocyte colony-stimulating factor or a blood transfusion. Although anorexia, nausea, fatigue, rash, pigmentation and aminotransferase elevation were also observed frequently in our study, most of these non-hematological toxicities were manageable with appropriate treatments. Therefore, it is considered that GS therapy in this study is tolerable for patients with metastatic pancreatic cancer.

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