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Review Article: Strategy for drug discovery at pharmaceutical companies

Proposal for the Breakdown of Increased Cancer Healthcare Cost and Its Improvement

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Technological progress in the field of cancer treatment can be expected to accelerate in the future, giving hope to such patients. At the same time, there is concern that cancer care will become more expensive. It is indispensable to minimize the economic burden of patients to deliver technological advances in treatment. It is important for the physician engaged in cancer care to recognize the economic burden of patients and to reduce this burden as much as possible. The Cancer Control Act was enacted in 2007 to promote work on cancer control using all the resources of the nation, and this should surely entail financial support. In order to take advantage of innovations in cancer care, reform of the payment system to lighten the economic burden of the patient would be a pressing necessity.

Key words: economic burden – cancer economics – cost of cancer – molecular targeted drugs – healthcare reform

EXPANDING MEDICAL EXPENSES OF CANCER

The national medical care expenditure in fiscal year 2010 in Japan announced at the end of September 2012 was 37 420 200 million yen, an increase of 3.9% compared with the previous fiscal year. The national income ratio, which was 8.1% in 2000, became 10.7%. The medical expenditure tends to increase sequentially when a slump in economic growth is prolonged. As for the medical care expenditure by age group, it was 55.4% for those 65 years old and older, 45.1% for those 70 years old and older and 33.3% for those 75 years old and older. These were 48.3, 37.4 and 25.1%, respectively, in 2000. Rapid aging of the population was found to be the major factor in the increase in medical care expenditures.

The medical care expenditure per capita was 292 200 yen, a record high. This generally represents an increase in each age group, and it is thought that technological progress is a major factor in the increase. The medical care expenditure for cancer in 2010 was 3 031 200 million yen. In total, 498 800 million yen were spent for colorectal cancer, 381 100 million yen for cancer of the trachea, bronchus and lung, 323 900 million yen for stomach cancer, 252 900 million yen for breast cancer and so on. The ratio of the cancer expenditure to the total medical expenditure was 11.2%. The growth rate of expenditures for cancer was 45.7% from 2000 to 2010, while that of the national medical care expenditure was 24.1% (Fig. 1). The increase in the cancer care expenditure is really remarkable.

In order to tackle with the high price of new technology and new therapeutic drugs, Central Social Insurance Medical Council in Japan has begun to discuss the possibility to introduce technology assessment in the actual public health insurance system. The point at issue is how to reduce health-care cost and to improve the quality at the same time. Some indicators such as cost-effectiveness and quality-adjusted life years is taken up for the discussion.

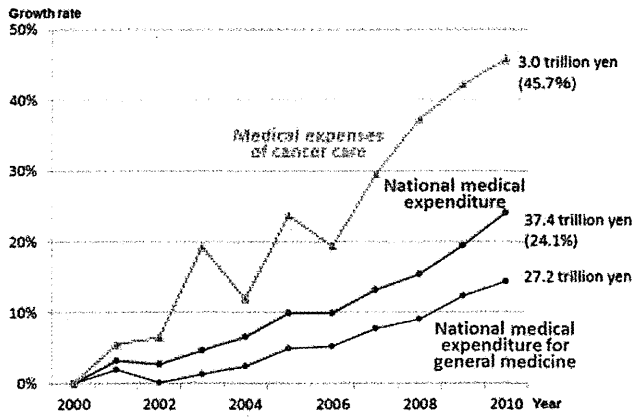

Figure 1. The trend of increase of cancer care expenses from the year 2000. The growth rate of expenditures for cancer was 45.7% from 2000 to 2010, while that of the national medical care expenditure was 24.1

INCREASING ECONOMIC BURDEN OF PATIENTS

Along with the increase in the national medical care expenditure, the economic burden of patients as well as the financial burden of the country became heavier. The co-payment for patients was raised from a fixed charge to 10% in 1984. The ratio of the patient's co-payment was raised from 10% to 20% in 1997 and from 20% to 30% in 2002. Thereafter, the co-payment of 30% (~15% for all ages) has continued. Since the medical care expenditure continued to increase and the co-payment ratio is always 30%, the actual economic burden for the patient increases constantly.

The increase in the cancer care expenditure largely resulted from the increase in the number of cancer patients along with the aging of the population. Simultaneously, rapid technical progress influences the increase in the cancer care expenditure to a great extent. Aging factor and other factors including technical progress have contributed in 46 and 54%, respectively, to the increase in the national medical care expenditure from fiscal year 2007–2008 according to the statistics of Ministry of Health, Labour and Welfare.

The cancer care expenditure per patient increased 9% for 5 years from 2002 through 2007, whereas the average annual salary has decreased 11% from 4.61 million yen in 2000 to 4.12 million yen in 2010 according to National Tax Agency 'Private salary investigation'. This means that the economic burden of patients has become heavier.

The actual situation of the economic burden of patients with cancer is not fully grasped. Therefore, we investigated 40 institutions such as university hospitals and cancer centers through the country (2010 through 2011). This was a self-completed survey asking patients with cancer to list the expenses related to cancer based on a household account book or on the receipts. Moreover, we got clinical information from physicians upon the approval of the patients and conducted a data linkage of the patient survey (1).

As a result, the average annual out-of-pocket expenses for cancer were 864 000 yen ($n = 2022$). The direct expenses of hospitalization, ambulatory care and transportation were 294 000 yen (applicable patients: 68.2%), 259 000 yen and 56 000 yen, respectively. For indirect expenses, the premium of private insurance and cost of alternative medicine were 380 000 yen (applicable patients: 55.0%) and 213 000 yen (32.3%), respectively (Fig. 2).

On the other hand, the refunds and benefits were 624 000 yen on average. The benefits from private insurance, medical refunds and tax refunds were 1 140 000 yen (applicable patients: 43.3%), 242 000 yen (48.2%), 62 000 yen (22.3%), respectively. The substantial economic burden when refunds and benefits were deducted from out-of-pocket expenses was 240 000 yen. Private insurance in Japan complements public insurance, and many patients are aided by this benefit.

For gastric cancer ($n = 158$), the out-of-pocket expenses and the refunds/benefits were 724 000 yen and 664 000 yen, respectively. These were 931 000 yen and 636 000 yen for colorectal cancer ($n = 244$), 1 102 000 yen and 681 000 yen for lung cancer ($n = 302$), 687 000 yen and 496 000 yen for breast cancer ($n = 773$), and 489 000 yen and 246 000 yen for prostate cancer ($n = 102$), respectively. The out-of-pocket expenses and the refunds/benefits differ considerably by types of cancer due to the large variety of treatments and prognosis and so forth.

The out-of-pocket expenses and the refunds/benefits were 1 217 000 yen and 652 000 yen for molecular targeted treatment ($n = 494$), and were 1 156 000 yen and 615 000 yen for the treatment of hematological malignancies, respectively. The out-of-pocket expenses (direct and indirect expenses) were 1 104 000 yen for chemotherapy using Trastuzumab ($n = 206$), 1 160 000 yen for Gefitinib ($n = 61$) 1 242 000 yen for Imatinib ($n = 213$), and 1 533 000 yen for Bevacizumab ($n = 160$), respectively.

DIFFERENCE IN BURDEN BY CLINICAL STAGE

The economic burden differs according to the clinical stage. The out-of-pocket expenses and the refunds/benefits were 610 000 yen and 509 000 yen in Stage I, 683 000 yen and 478 000 yen Stage II, 982 000 yen and 754 000 yen in Stage III, and 1 284 000 yen and 778 000 yen in Stage IV, respectively. The expenditures for alternative medicine and supplements tended to increase with the seriousness of the disease. The annual length of hospital stay was 20.6 days in Stage I, 23.3 days in Stage II, 37.1 days in Stage III and 44.3 days in Stage IV, respectively. The number of visits to hospital was 14.2 times in Stage I, 18.9 times in Stage II, 22.4 times in Stage III, and 24.9 times Stage IV, respectively. Looking at this according to the types of therapy, the length of stay was 27.8 days for surgery, 39.9 days for chemotherapy and 32.6 days for radiotherapy. The number of visits was 18.6 times for surgery, 24.6 times for chemotherapy and 29.3 times for radiotherapy.

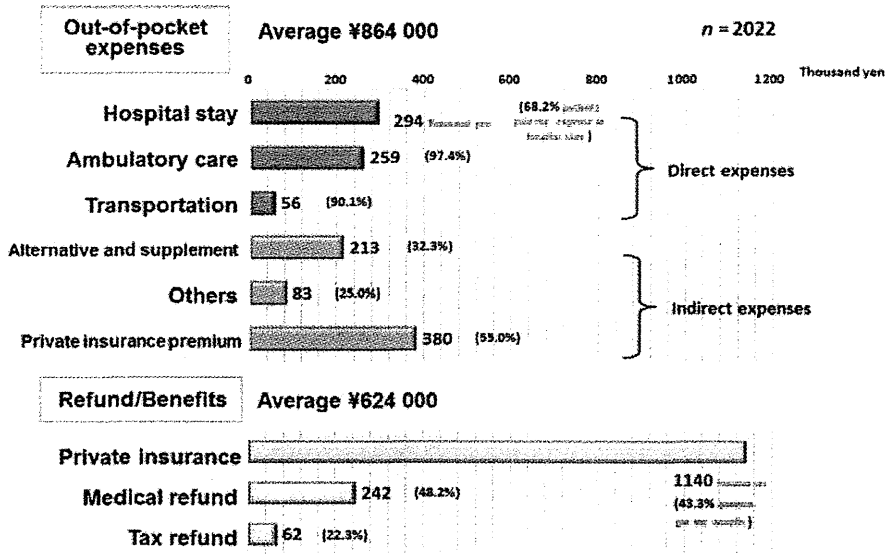

Figure 2. Annual economic burden of cancer patient. The average annual out-of-pocket expenses for cancer were 864 000 yen and the refunds and benefits were 624 000.

The economic burden also differed according to the ratio of the patient's co-payment. The out-of-pocket expenses and the refunds/benefits were 934 000 yen and 746 000 yen with a co-payment of 30% ($n = 1443$ average age 58.5 years old), respectively. In other words, the actual burden was 188 000 yen. However, these were 672 000 yen and 275 000 yen with a co-payment of 10% ($n = 554$, 75.4 years old). In this case, the balance was 397 000 yen, which was heavier than burden with a co-payment of 30%. In case of a co-payment of 10%, the average benefit from private insurance (683 000 yen on average for 32.4% of the patients) and the medical refund (86 000 yen for 54.8% of the patients) are much smaller than that of a co-payment of 30%.

Around 69% of the patients had economic worries ($n = 2037$). The mean out-of-pocket expense (752 000 yen) of the patients without economic worries was three-fourths that of the patients (987 000 yen) with economic worries (Fig. 3). In the viewpoint of promoting work, if the length of stay is shortened and the number of hospital visits is decreased, the patients with cancer would have more working opportunities. For example, in patients with breast cancer ($n = 774$), the average length of stay was 14.1 days and the number of visits was 20.4 times. If the hospitalization included Saturday and Sunday for 4 days and ended on a half day, the suspension of work due to treatments would be almost equal to annual paid holidays.

DECLINING THE TREATMENT DUE TO ECONOMIC REASONS

According to our survey, three-fourths of the patients with colorectal cancer felt that the medical expenses under public insurance were heavy ($n = 232$). Half of the above patients felt that the premium of private insurance and the costs of alternative medicine were also heavy. Many patients think that the indirect expenses are crucial. Sixty percent of patients with colorectal cancer were obliged to withdraw deposits and savings, and 10% managed to pay the medical costs by borrowing from a family member or relative ($n = 249$). In our survey, the average age of patients with colorectal cancer was 64.4 years and a pension was the sole regular income for many patients. For one-third of the above patients, the household income was between 1 million and 3 million yen. For 40% of the above patients, the household savings were less than 7 million yen.

Although medical treatment cannot be denied for economic reasons under Japanese universal health insurance system, patients who refused an expensive therapy have recently increased. According to our survey for physicians engaged in cancer care ($n = 1176$, clinical experience: 17.8 years), 1.6 inpatients and 1.5 outpatients per month gave up the most appropriate treatment due to some economic reason.

Sixteen percent of the above patients had to cancel the scheduled treatment, 56% could not avoid changing the treatment and 13% were obliged to interrupt the treatment. It is an extremely serious situation for patients, and also for their physicians, when patients must forego necessary treatments, especially considering that refunds are available expensive medical treatments. Since molecular-targeted drugs are expensive in general, it is not rare to modify or withdraw these drugs such as Bevacizumab or Sorafenib for the treatment of solid tumors and Rituximab or Imatinib for hematological malignancies. In the case of Bevacizumab, for instance, a planned regimen such as Bevacizmab + XELOX was modified to XELOX. In the same manner, some regimens were modified from Bevacizmab + mFOLFOX6 to mFOLFOX6, and from Bevacizmab + FOLFIRI to FOLFIRI.

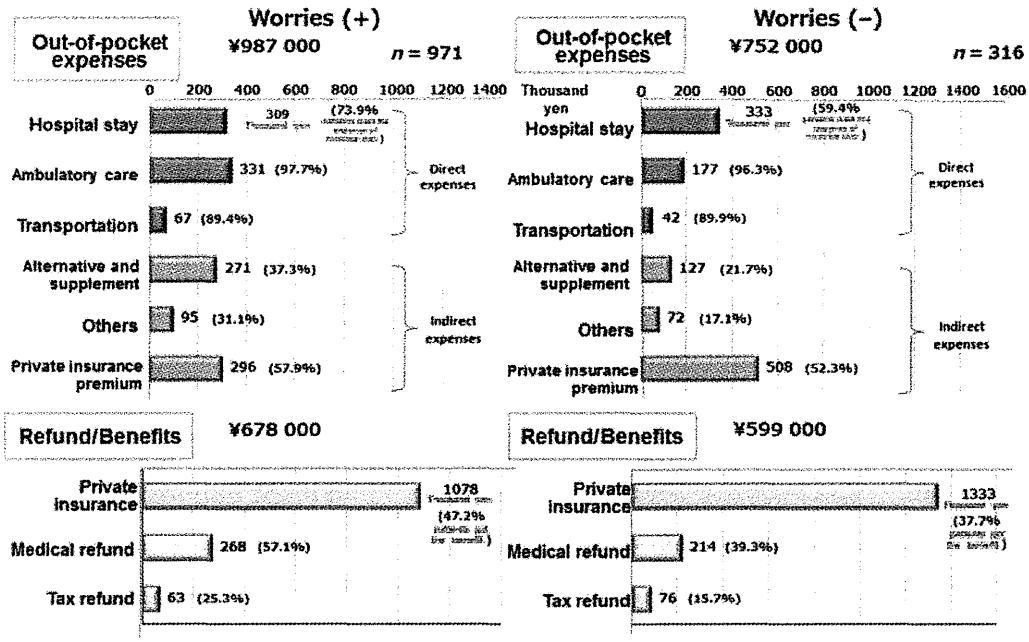

Figure 3. Annual economic burden of cancer patient by worries about economic problems. The mean out-of-pocket expense of patients without economic worries was three-fourths that of the patients with economic worries.

We calculated the change in drug costs on the basis of the payment system for medical services in 2011 (the standard treatment for a male patient of 60 kg and 165 cm) in the above three cases. Drug costs were decreased by 48.6%, from 468 000 yen to 228 000 yen, by 49.8%, from 299 000 yen to 149 000 yen, and by 35.4%, from 232 000 yen to 82 000 yen, respectively. Given the payment system, if one half of the current drug costs is supported by a second or third party, more patients would be able to undergo optimal treatment.

IMPORTANT ROLE OF MEDICAL REFUND SYSTEM

There are limits to the expenses patients must pay based on their income. The medical refund system is a safety net that complements the health insurance system (co-payment of 10–30% by the patient). The government expenditure for medical refunds has doubled during the 8 years from 2000 through 2008 (1713 billion yen), suggesting that the economic burden on patients has been increasing. The medical refund system was founded in 1973, and many regulations were introduced afterwards. User cannot easily understand this complicated system. However, the detailed rules of the system have come to be understood by patients, since this system is requested by the patients the number of users has increased. This system is explained in detail when required in the consultation support center of cancer center hospitals. Forty-eight percent of patients with cancer and 80% of patients administered molecular-targeted treatment applied for this system, which has recently become indispensable. We examined how the medical refund system reduces patients' payments using the survey data. We found that this system lightens the patients' burden by 32.5% on average ($n = 686$) (Fig. 4). These are 35.4% in patients with colorectal cancer and 36.6% in patients from 40 to 49 years old.

MEASURES AGAINST RISING COST OF CANCER TREATMENT

There are many requests for relief from the economic burden from patients with cancer, who want the cost of anticancer drugs to be reduced, the ceiling for reimbursement to be lowered, the percentage of co-payment to be lower than for other diseases and that more information about the economic burden should be given to patients and so on ($n = 236$). Measures corresponding to the patients' suffering from the economic burden of treatment are very urgent. The problem of so-called 'economic refugees with cancer' (patients who cannot undergo the adequate treatment for economic reasons) might be addressed along with the accelerating technological progress.

These measures could be broken down into three levels: physicians' consideration in the clinical setting, better operation of the actual system and drastic healthcare reform. The first level includes the promotion of ambulatory care as an alternative to hospitalization, shortening the duration of hospitalization, reducing excessive testing and medication, the use of cheaper generic drugs and adequate explanation about the costs. The second level includes reductions in the ceiling

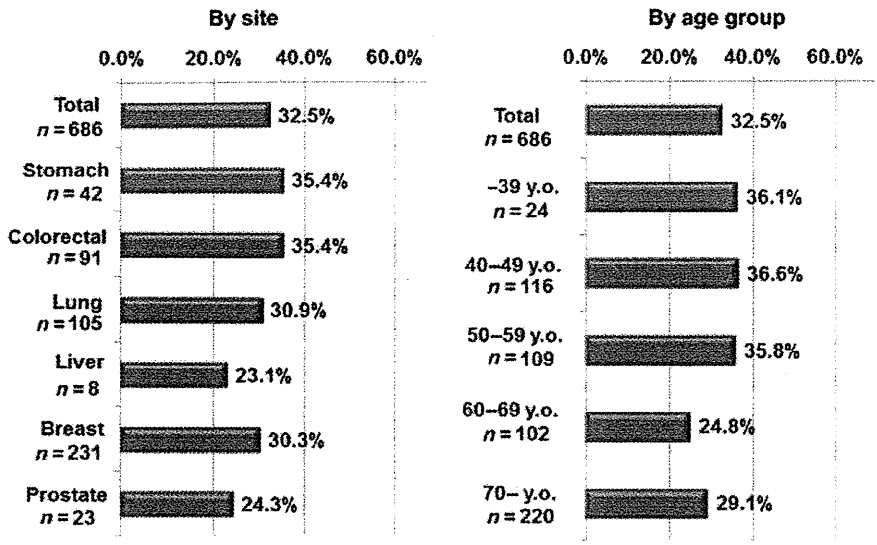

Figure 4. Percent reduce of the patients' payments with medical refund system. The medical refund system lightens the patients' burden by 32.5% on average. y.o., years old.

for reimbursement and improvement of the so-called 'drug lag' (shortening the approval process for new drugs) and 'device lag' (that of new technology). A few patients are obliged to the new drugs by way of the personal import on their own expense.

For the third level, it is necessary to review the proper percentage of co-payments depending not only on age but also on the seriousness or other characteristics of the disease to relieve the excessive economic burden of the patients. The national income has been decreasing while medical costs per person have been increasing for the past decade and there is surely a limit to the economic relief that can be provided by the medical refund system. This is because the payment of medical refunds has greatly expanded and the government will suffer from insufficient funds.

Information about patients' out-of-pocket expenses in other countries would be useful for our healthcare reform, although health insurance systems differ country by country and a simple comparison might lead to misunderstandings. Medical care is free of charge as a rule in such countries as the UK, Canada and Australia (excluding drug costs). The out-of-pocket expenses of a patient is 10 euros per day for hospitalization and 10 euros per quarter for ambulatory care (it is free of charge if there is a letter of introduction) in Germany. There is an upper limit of 80 krona per day (~9600 yen) for hospitalization and an upper limit of 900 krona per year for ambulatory care in Sweden. The economic burden of a patient is rather light in these countries.

The percentage of out-of-pocket payments is 20% for hospitalization and 30% for ambulatory care in France, whose system resembles that of Japan. However, some private insurance can bridge most of the payment gaps, and medical care for 30 diseases including cancer is free of charge. This is an important example of how the heavy economic burden of long-term and expensive treatments can be avoided by patients. That is, it turns out that the out-of-pocket payments in Japan act at a particularly high level for developed countries. It is extremely important to secure necessary healthcare resources from and to drastically rationalize the distribution of medical expenditures. Such reform of the current insurance system is inevitable because of the need to cope with constantly advancing innovation. Healthcare systems in some western countries have introduced the concept of priority (so-called 'triage' not only in emergency medicine but also in general medicine), which serve as a reference *for* Japan.

The total sum of out-of-pocket payments by patients with cancer in Japan comes to 461 billion yen per year based on the data of our survey. Therefore, making cancer treatment free of charge would be possible in Japan if an additional 500 billion yen in public spending were made available. There is little risk of moral hazard (increase of the number of patients and medical expenditures caused by the lack of fee) since the diagnosis of cancer is concrete. Financial support depending on the type of disease is more rational than that depending on the age group (such as charge-free medical care for the elderly ~40 years ago), because the elderly vary in health status significantly even at the same age.

The average age of patients with cancer exceeds 60 years old. The income is restricted to a pension in many cases and the out-of-pocket expenses for cancer treatment are often covered by drawing on savings. When looking at the annual household income (tax included), 31% of the patients earned 1~3 million yen or less and more than half is <5 million yen ($n = 2928$, average age 61.7 years old). As for the amount of household savings, in 40% it was <7 million yen and in half it was <10 million yen. Many senior citizens tend to reduce daily living expenses on the preparation for the high probability suffering from serious illness in the future. The domestic demand is reduced if those of middle

and advanced age, which occupy the majority of the population, refrain from consumption because of worries about future illness. It is essential to stabilize the pension system, but the solution to this problem will likely take time before anxiety about the future is alleviated. Relief from the economic burden of cancer care must be a reasonable certainly for the elderly, and it would be one of the most cost-effective measures to implement.

CONCLUSION

Technological progress in the field of cancer treatment can be expected to accelerate in the future giving hope to such patients. At the same time, there is concern that cancer care will become more expensive. It is indispensable to minimize the economic burden of patients to deliver technological advances in treatment. The economic burden of the patient might influence the outcome of treatment, and the costs would therefore be an important element in high-quality cancer care, as ASCO (American Society of Clinical Oncology) noted (2). It is important for the physician engaged in cancer care to recognize the economic burden of patients and to reduce this burden as much as possible. The Cancer Control Act was enacted in 2007 to promote work on cancer control using all the resources of the nation, and this should surely entail financial support. In order to take advantage of innovations in cancer care, reform of the payment system to lighten the economic burden of the patient would be a pressing necessity.

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Conflict of interest statement

None declared.

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Safety Verification Trials of mFOLFIRI and Sequential Irinotecan + Bevacizumab as First- or Second-Line Therapies for Metastatic Colorectal Cancer in Japanese Patients

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Key Words
Advanced colorectal cancer · Irinotecan · Bevacizumab · S-1 · Randomized trial

Abstract
Objective: S-1 is effective in sequential combination with irinotecan (IRIS) in treating metastatic colorectal cancer. We conducted a randomized phase II trial of modified leucovorin, fluorouracil and irinotecan (mFOLFIRI) + bevacizumab and sequential IRIS + bevacizumab as first- or second-line therapies. ***Methods:*** Sixty metastatic colorectal cancer patients were randomly assigned to receive mFOLFIRI + bevacizumab or sequential IRIS + bevacizumab (7.5 mg/kg of bevacizumab and 150 mg/m^2 of irinitecan, and 80 mg/m^2/day of S-1 orally from day 3 until day 16 as a 3-week course). The primary endpoint was the safety of each method until week 12, with the secondary endpoint being the comparison of the safety and efficacy of the two methods. ***Results:*** The safety of the two treatments was comparable, except that G3 anorexia and diarrhoea were less frequent with sequential IRIS + bevacizumab. The overall response rate was 62% [95% confidence interval (CI) 40.1–79.8] versus 72% (95% CI 50.6–86.2), and progression-free survival was 324 days (95% CI 247–475) versus 345 days (95% CI 312–594) with mFOLFIRI + bevacizumab versus IRIS + bevacizumab, respectively. ***Conclusion:*** Sequential IRIS + bevacizumab is a safe and effective method of systemic chemotherapy against metastatic colorectal cancer and is compatible with mFOLFIRI + bevacizumab.

Introduction

Over the past 10 years, as a result of multidisciplinary therapies including systemic chemotherapy, there has been a dramatic improvement in the success of treat-

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ments against unresectable and/or recurrent colorectal cancer [1]. Particularly, based on the results of several clinical trials, bevacizumab was shown to extend progression-free survival (PFS) when used in combination with other chemotherapies including irinotecan, fluorouracil and leucovorin [2], leucovorin, fluorouracil and oxaliplatin (FOLFOX) [3], leucovorin, fluorouracil and irinotecan (FOLFIRI) [4], and 5-fluorouracil and leucovorin (5-FU/LV) [5]. These results are further supported by large-scale observational studies [6, 7]; however, in standard chemotherapy treatments, as often represented by either FOLFOX or FOLFIRI, placement of a peripherally inserted central venous port (CV port) is required for continuous 5-FU infusion. The usage of CV ports can cause complications, including infections and thrombosis, resulting in decreasing the patient's quality of life [8, 9].

In consideration of these factors, chemotherapy regimens using oral fluoropyrimidines rather than continuous 5-FU infusion must be developed. The CapeOX regimen, which uses capecitabine, an oral fluoropyrimidine pro-drug of 5-FU rather than 5-FU/LV, plus oxaliplatin, has identical therapeutic effects to FOLFOX. Favourable results were also observed when used in combination with bevacizumab [10]. However, because of severe gastrointestinal toxicity associated with capecitabine in combination with irinotecan (CapeIRI or XELIRI), an effective alternative treatment to FOLFIRI has yet to be developed [4].

S-1 is a combination of tegafur, a pro-drug of 5-FU that consists of oral fluoropyrimidines, gimeracil (5-chloro-2,4-dihydoroxypyridine) and oteracil (potassium oxonate) at a molar ratio of 1:0.4:1 [11]. Gimeracil has a reversible competitive inhibitory effect on dihydropyrimidine dehydrogenase, a rate-limiting enzyme involved in the metabolic degradation of 5-FU. Oteracil reduces gastrointestinal toxicity and is effective against a wide range of carcinomas. Against metastatic colorectal cancer, S-1 showed a response rate of 39.5%, a PFS of 5.4 months and an overall survival time of 11.9 months when used as a monotherapy [12]. Because S-1 is expected to replace 5-FU/LV, there have been several prospective clinical trials in Japan using S-1 in combination with oxaliplatin (L-OHP or SOX) [13]. Clinical trials of S-1 combined with irinotecan (IRIS) were also conducted with various schedules or dosage regimens [14–16]. Among these, Yoshioka et al. [15] conducted phase I/II trials of sequential IRIS and the combined treatment of staggered irinotecan and S-1. These clinical trials were performed in order to avoid decreased therapeutic effects and increased toxicities caused by the inhibitory effect of 5-FU and its metabolites on the bioactivation of SN-38 from irinotecan [17, 18]. The authors reported on how this treatment regimen effectively avoided toxicity and rivaled the efficacy of previous FOLFIRI treatments; however, because the introduction of molecular targeted drugs in Japan was delayed, no studies were performed on the safety and efficacy of sequential IRIS in combination with bevacizumab. Thus, we report on the respective safety of sequential IRIS + bevacizumab and modified FOLFIRI (mFOLFIRI) + bevacizumab therapies against unresectable colorectal cancer. A secondary comparative study on the safety and efficacy of both therapies was also performed.

Patients and Methods

Patient Eligibility

The eligibility criteria were as follows: (1) patients histologically diagnosed with colorectal cancer; (2) patients with either an unresectable primary tumour or distal metastatic tumours; (3) an Eastern Cooperative Oncology Group performance status of 0 or 1; (4) the previous chemotherapy regimen had to be ≤1; (5) patients of post-operative adjuvant chemotherapy >6 months since last administration of drugs; (6) in the case of second-line therapy, first-line therapy had to be FOLFOX treatment; (7) internal organ function maintained, i.e. white blood cell count of 3,500–12,000/μl, platelet count ≥100,000/μl, aspartate aminotransferase (AST) ≤100 IU/l, alanine aminotransferase (ALT) ≤100 IU/l, total bilirubin ≤ 1.5 mg/dl, serum creatinine ≤1.2 mg/dl, serum creatinine clearance as estimated by Cockcroft-Gault equation ≥50 ml/min; (8) survival expected to be at least ≥3 months; and (9) written informed consent obtained from the patient for trial participation.

Exclusion criteria were as follows: (1) a history of abdominal irradiation; (2) any complications, such as intestinal paralysis, intestinal obstruction, poorly controlled diabetes, poorly controlled hypertension, unstable angina, hepatic cirrhosis, interstitial pneumonia, pulmonary fibrosis or severe pulmonary emphysema; (3) body cavity fluid retention requiring treatment; (4) poorly controlled peptic ulcerations; (5) concomitant gastrointestinal perforation or a history of perforation within 1 year prior to registration; (6) brain tumours or cerebral metastases confirmed on imaging; (7) concomitant symptoms of cerebrovascular nerve damage or any type of cardiac disease requiring treatment; (8) surgical treatment within 4 weeks prior to registration; (9) a bleeding tendency, coagulation disorder or excessive clotting factors; (10) awaiting or on treatment for chronic inflammatory disease such as rheumatoid arthritis, with any drugs that inhibit platelet function (aspirin or non-steroidal anti-inflammatory drugs); (11) women who are pregnant, may be pregnant, wish to become pregnant or are lactating; (12) men who wish their partner to become pregnant; (13) patients using irinotecan as post-operative adjuvant chemotherapy.

Treatment Methods

In the sequential IRIS + bevacizumab treatment regimen, on day 1, 7.5 mg/kg of bevacizumab was administered for >30 min, and 150 mg/m^2 of irinotecan was administered continuously for >90 min. Then, for the 2-week period from days 3 to 16, divided doses of S-1 were administered twice daily. The dosage of S-1 was as follows: body surface area (BSA) <1.25 m^2, 80 mg/day; BSA 1.25–1.5 m^2, 100 mg/day, and BSA >1.5 m^2, 120 mg/day as a 3-week course. Dosage for the mFOLFIRI + bevacizumab treatment regimen was as follows: 5 mg/kg of bevacizumab, 150 mg/m^2 of irinotecan, 200 mg/m^2 of L-leucovorin, 400 mg/m^2 of 5-FU by rapid intravenous infusion on day 1, and 2,400 mg/m^2 of 5-FU for 46 h by continuous intravenous infusion as a 2-week course. The treatment protocol period was set at 12 weeks in both groups, and treatment was continued until the criteria for discontinuation of the trial were met.

The criteria for commencement of treatment in each course were as follows: white blood cell count ≥3,000/μl, platelet count ≥75,000/μl (mFOLFIRI + bevacizumab) or ≥100,000/μl (IRIS + bevacizumab), AST ≤100 IU/l, ALT ≤100 IU/l, total bilirubin ≤1.5 mg/dl, and serum creatinine ≤1.2 mg/dl. In addition, diarrhoea of grade 0 and improvement in any other non-haematologic toxicity (excluding constipation, loss of appetite, loss of hair, chromatosis and dysgeusia) of grade ≤1 was required. In patients where the criteria for commencement of treatment were not met, treatment was delayed until all necessary requirements were completely satisfied. Treatment was discontinued in those patients where the criteria for commencement of treatment were not met even after a delay of ≥3 weeks.

The criteria common to both groups for discontinuation of bevacizumab treatment were as follows: (1) any grade of haemoptysis, gastrointestinal perforation, reversible leucoencephalopathy syndrome; (2) grade ≥3 thromboembolism, haemorrhage or hypersensitivity reaction, and (3) grade 4 proteinuria or hypertension. In patients with grade 2 haemorrhage, treatment was withdrawn until improvement to grade 0, and treatment was discontinued in patients where grade 2 haemorrhage recurred. Treatment was discontinued in patients with grade 3 hypertension that could not be controlled by medication. Treatment was withdrawn in the following situation: patients with grade 2 or 3 proteinuria until proteinuria was ≤2 g as determined by 24-hour urine collection analyses, with grade 3 or 4 liver dysfunction until improvement to either grade 1 or baseline, and in instances of recurrence.

In the IRIS group, S-1 administration was stopped if any of the following adverse effects occurred during the course: (1) grade ≥3 leucopenia or neutropenia in addition to other grade ≥3 non-haematological toxicity, until patient recovery; (2) grade ≥2 thrombocytopenia, diarrhoea, stomatitis, nausea or vomiting; (3) serum creatinine ≥1.5× the upper limit of normal, and (4) AST or ALT ≥100 IU/l. Any patients exhibiting grade ≥4 leucopenia or neutropenia, grade ≥3 thrombocytopenia, diarrhoea, stomatitis, nausea or vomiting, non-haematological toxicity, or AST or ALT ≥200 IU/l during the study were administered a lower dosage of IRIS in the next course of treatment. The low dosage of S-1 (level 1) was 50 mg/day for BSA <1.25 m^2, 80 mg/day for BSA 1.25–1.50 m^2, and 100 mg/day for BSA >1.5 m^2. For irinotecan, level 1 was 120 mg/m^2 and level 2 was 100 mg/m^2; no increase was made once dosage decreased. Also, in the mFOLFIRI + bevacizumab regimen, dosage was reduced in patients with grade ≥4 leucopenia or neutropenia, grade ≥3 thrombocytopenia, diarrhoea, stomatitis, nausea or vomiting or non-haematological toxicity as follows: 120 mg/m^2 of irinotecan and 200 mg/m^2 of 5-FU (bolus) for level 1, and 100 mg/m^2 of irinotecan, 200 mg/m^2 of 5-FU (bolus) and 2,000 mg/m^2 of 5-FU (infusion) for level 2.

With regard to safety data, the patients' health status was observed and blood samples were tested during weekly medical examinations by the attending physician until 4 weeks after commencing treatment and repeated after the fifth week at the start of each new course of treatment. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events version 3.0, and effectiveness was observed according to the Response Evaluation Criteria in Solid Tumors 1.0. Computed tomographic scans were performed every 6 weeks. Effectiveness was judged comprehensively using blinded tests on the treatment methods by 3 or more physicians not including primary physicians.

Interim Analysis about Safety

After 3 cases have been registered in each group, registration was stopped to evaluate the safety of the two treatments (step 1). After the confirmation of the safety of the two treatments by the efficacy and safety evaluation committee, registration was reopened with 60 patients enrolled (30 per group; step 2).

Statistical Analysis

While attempting to detect a frequency of ≥10% with 95% probability for the occurrence of adverse events, we determined that the sample size would include 30 patients in each experimental group or 60 patients overall in the two experimental groups [19]. Patients' background, safety and efficacy data were summarized as frequencies and percentages. The χ^2 test was used to compare between groups, while the Kaplan-Meier method was used to analyse PFS.

Results

Patient Background

From November 2007 to February 2010, 60 patients were registered from the 12 institutes of the Tohoku Clinical Oncology Research and Education Society. These patients were randomly assigned to either the mFOLFIRI + bevacizumab or sequential IRIS + bevacizumab groups, with 30 patients in each group. Patient backgrounds are presented in table 1; the median age was 62.5 (range 46–77) and 62 years (range 31–73) in the mFOLFIRI + bevacizumab and sequential IRIS + bevacizumab group, respectively. Many patients were receiving first-line treatment (24 patients in the mFOLFIRI + bevacizumab group and 23 patients in the IRIS + bevacizumab group). No significant bias was seen between the two groups.

Safety Verification Test (Step 1)

Step 1 of this trial was to register 3 patients at a time into the two experimental chemotherapy regimen groups and evaluate the initial safety for 12 weeks. The last patient was registered in April 2008 when patient registration was temporarily suspended and initial safety was assessed. Except for 1 patient in the mFOLFIRI + bevacizumab group with gastrointestinal perforation (G3), no other severe adverse events occurred. Because international phase III and verification trials in combination with FOLFOX treatment in a Japanese population cite gastrointestinal perforation as an expected adverse event, the efficacy and safety evaluation committee recommended proceeding to step 2 while maintaining utmost vigilance with regard to patient safety.

Safety Verification Trial (Step 2)

By February 2010, 60 patients had been registered in the study, including the 6 patients from step 1 and were randomly allocated to the two experimental groups (table 1). Although one adverse event of gastrointestinal perforation (G5) was observed in the mFOLFIRI + bevacizumab group, this was determined to be due to progression of an underlying disease (table 2) and not due to the experimental treatment. With regard to G3/4 haematological toxicities in the mFOLFIRI + bevacizumab and sequential IRIS + bevacizumab treatment groups, neutropenia was seen at a rate of 48 and 38%, respectively. Although statistical differences were not observed, G3/4 gastrointestinal toxicities were more frequent in the mFOLFIRI + bevacizumab group than in the sequential IRIS + bevacizumab group (anorexia 17.9 and 3.4%, nausea 7.1 and 0%, diarrhoea 14.3 and 6.9%, respectively). G3/4 severity in hypertension, which is the representative adverse event of bevacizumab, was confirmed as 3.6% in the mFOLFIRI + bevacizumab group, whereas it was not observed in the sequential IRIS + bevacizumab group. No patient experienced severe proteinurea, thrombosis or haemorrhage in either group.

Comparison of Efficacy

The treatment methods were blind, and efficacy was compared by judging the response rate with a 3-person decision committee. The overall response rate (ORR) in the mFOLFIRI + bevacizumab group versus the sequential IRIS + bevacizumab group was 61.5% [95% confidence interval (CI) 40–80] and 72.0% (95% CI 51–86), respectively (table 3). Two patients showed complete response in the sequential IRIS + bevacizumab group. The median PFS was 324 days (95% CI 247–475) in the mFOLFIRI + bevacizumab group and 345 days (95% CI 312–594) in the sequential IRIS + bevacizumab group (fig. 1). Statistical significance was not observed between the two groups (p = 0.71).

Table 1. Characteristics of patients

	mFOLFIRI + bevacizumab (n = 30)	IRIS + bevacizumab (n = 30)
Age, years		
Median	62.5	62
Range	46–77	31–73
Males/females	18/12	17/13
ECOG performance status		
0	24	27
1	6	3
Primary legion		
Colon	17	17
Rectum	12	13
Both	1	0
Cancer		
Advanced	22	20
Recurrent	8	10
Histology		
Well	7	7
Moderately	20	22
Poor	2	0
Other	1	1
Primary site		
Yes	5	6
No	25	24
Number of metastases		
1	17	16
2	9	10
3	4	4
Adjuvant chemotherapy		
Yes	5	7
No	25	23
Prior chemotherapy		
Yes	24	25
No	6	5

ECOG = Eastern Cooperative Oncology Group.

Discussion

Systemic chemotherapy against unresectable or recurrent colorectal cancer was developed on the basis of the successful combination therapy of 5-FU and L-leucovorin. Continuous 5-FU infusion and cytotoxic drugs (e.g. irinotecan and L-OHP, as well as other molecular target-

Table 2. Adverse events of the two treatments

Adverse event	mFOLFIRI + bevacizumab							IRIS + bevacizumab							p value (χ^2 test; G3,4)
	G0	G1	G2	G3	G4	G5	grade >3, %	G0	G1	G2	G3	G4	G5	grade >3, %	
Non-haematological															
Anorexia	10	5	8	5			17.9	13	10	5	1			3.4	0.076
Nausea	10	7	9	2			7.1	16	11	2				0.0	0.143
Vomiting	20	6	1	1			3.6	28			1			3.4	0.980
Diarrhoea	12	12		4			14.3	15	11	1	2			6.9	0.364
Mucositis	17	10	1				0.0	23	6					0.0	(-)
Fatigue	14	8	4	2			7.1	17	9	3				0.0	0.143
GI perforation	26			1		1	7.1	29						0.0	0.143
Bleeding	20	7	1				0.0	21	8					0.0	(-)
Hypertension	20	3	2	1			3.6	24	2	1				0.0	0.304
Proteinuria	20	3	2				0.0	22	2	3				0.0	(-)
Haematological															
Leucopenia	5	6	12	4			14.3	12	3	9	5			17.2	0.409
Neutropenia	3[1]		11	8	5		48.1	12[1]		6	7	4		37.9	0.598
Thrombopenia	23	4					0.0	22	6		1			3.4	0.286

GI = Gastrointestinal. [1] Frequency of G0 and G1.

Table 3. Overall response of the two treatments

	mFOLFIRI + bevacizumab	IRIS + bevacizumab
CR	0	2
PR	16	16
SD	8	5
PD	2	2
NE	4	5
Total	30	30
RR, %	61.5 (40.1–79.8)	72.0 (CI 50.6–86.2)

Figures in parentheses are 95% CIs.
CR = Complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluated.

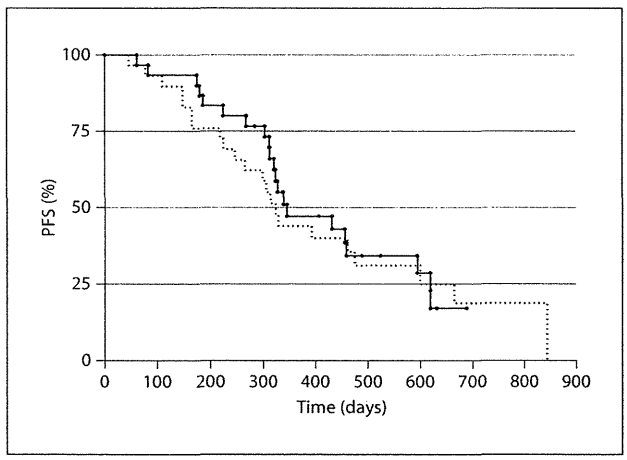

Fig. 1. Kaplan-Meier PFS curves of patients with metastatic colorectal cancer treated with mFOLFIRI + bevacizumab (dotted line) and IRIS + bevacizumab (solid line).

ed drugs, such as bevacizumab, cetuximab and panitumumab) are used concomitantly or sequentially to yield a median survival time that exceeds 2 years; however, continuous 5-FU infusion necessitates the insertion of a peripherally inserted central catheter or CV port, which can increase infection and thromboembolism risks. In order to circumvent these drawbacks, novel treatment options with oral fluoropyrimidines are being developed to replace the need for 5-FU infusions. The oral fluoropyrimidine S-1 exhibits a lower frequency of diarrhoea and hand-foot syndrome when compared with capecitabine, and S-1 has a higher tolerance level among Japanese people. Therefore, treatments such as SOX and IRIS are being developed in Japan to replace FOLFOX and FOLFIRI therapies, and it has been suggested that S-1 may be

able to replace 5-FU/LV [12–14]. Furthermore, because molecular targeted drugs, such as bevacizumab, cetuximab and panitumumab, have been introduced into routine clinical use in Japan, it has become important to evaluate the safety and efficacy of combined therapies on the basis of these drugs and on the new oral fluoropyrimidines.

Prior to this study, we tested the safety and efficacy of sequential IRIS therapy, which we found to have a low toxicity and high efficacy [13]. In this study, among patients with G3 or higher haematological toxicities, no significant differences between the two groups were observed with regard to neutropenia and/or leucopenia, although a lower trend was observed in the sequential IRIS + bevacizumab group. Muro et al. [16] performed a phase II/III trial comparing mFOLFIRI with irinotecan + S-1 therapy as a second line of treatment for patients with unresectable recurrent colorectal cancer. Although their administration method differed from our sequential IRIS therapy, as Muro et al. [16] did not use bevacizumab in their study, the frequency of G3/4 neutropenia in the mFOLFIRI (150 mg/m^2/2 weeks of irinotecan) and IRIS groups showed a similar trend to our data (52.1 and 36.2%, respectively), indicating that IRIS exhibits less neutropenic toxicity.

The incidence of gastrointestinal toxicity observed in this study in the mFOLFIRI + bevacizumab group was nearly identical to that in the FOLFIRI group (43.2–53.6%) as reported by a BICC-C study [4]. As with haematological toxicities, the frequency of non-haematological toxicity was lower in the sequential IRIS + bevacizumab group than in the mFOLFIRI + bevacizumab group. Furthermore, the frequency of reported gastrointestinal toxicities, such as loss of appetite (11%) and diarrhoea (20.5%), in the sequential IRIS + bevacizumab group of our study tended to be lower than that in the IRIS group in the study of Muro et al. [16]. This difference may be due to the following reasons: (1) all patients in the study of Muro et al. [16] were undergoing second-line treatment, and (2) the different administration method used placed a greater emphasis on irinotecan dose intensity than our sequential IRIS method. Muro et al. [16] also mentioned that raising the dose intensity of irinotecan was among the effective strategies for patients resistant to oxaliplatin-based chemotherapy; however, with regard to these adverse events, we believe that raising the dose intensity of S-1 rather than that of irinotecan is the better strategy for first-line treatment with regard to safety. Finally, as regards efficacy, the median PFS in both groups was about nearly a year. Although the number of patients in the current study was small, the level of efficacy seems to be higher than that in previous studies. The data on overall survival time are currently being analysed in a follow-up study.

Recently, Yamada et al. [20] reported the results of a phase II study on IRIS combined with bevacizumab (SIRB study). In the SIRB regimen, S-1 is administered on days 1–14 of a 21-day cycle, but the dose intensity of S-1, irinotecan and bevacizumab was equivalent to that of the sequential IRIS + bevacizumab regimen. Toxicity in the SIRB regimen was low and manageable (G3/4 neutropenia 26%, G3/4 anorexia 12%, G3/4 diarrhoea 8%). The ORR was 67% (95% CI 52.1–79.1) and the median PFS was 373 days (95% CI 299–440), which is comparable with our sequential IRIS + bevacizumab therapy.

From these results, we concluded that the combination of S-1, irinotecan and bevacizumab could be an effective primary therapy in Japanese patients, compared with mFOLFIRI + bevacizumab. Moreover, this regimen could reduce the risk of infection because it does not require a CV port. Therefore, sequential IRIS + bevacizumab therapy, a very promising treatment method, should be developed further in a larger randomized clinical trial. We are currently in the process of planning a phase III clinical trial in Japan comparing IRIS + bevacizumab with CapOX/FOLFOX + bevacizumab.

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前立腺がんの地域連携クリティカルパスにおけるバリアンス分析

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要旨：2007年11月から千葉県がんセンター泌尿器科は，千葉県内の泌尿器科開業医師との地域医療連携を開始するにあたり泌尿器がんの地域連携クリティカルパスを作成した。2011年10月現在，前立腺がん5種のクリティカルパスを運用しており症例数は1,460例であった。今回われわれは，2007年11月から2008年10月までの1年間に3種類の前立腺がんクリティカルパスが適応となった248例を対象として全例のバリアンス分析を行った。運用成績としてはクリティカルパス適応継続例が213例（86%），バリアンス例が35例（14%）であった。前立腺がん3種類のクリティカルパスのアウトカム設定条件は適切であったと考えられた。しかしバリアンス例の中には「連携から外れた症例」が23例（9%）みられており，クリティカルパスのアウトカム設定に診療連携の継続を追加することが必要と思われた。

key words　地域連携クリティカルパス，前立腺がん，バリアンス

はじめに

2007年のがん対策推進基本計画およびがん診療連携拠点病院の指定要件の見直しに伴い，がん診療連携拠点病院では5大がんを中心とした地域連携クリティカルパスの整備が求められている[1, 2]。

千葉県がんセンター泌尿器科では拠点病院に集中する患者数の緩和を目的に，主に千葉県内の泌尿器科開業医と医療連携をすすめる方法を模索していた。そこで前立腺特異抗原（PSA）を用いた前立腺がん地域連携クリティカルパスを3種類開発した[3]。開始時期は2007年11月で，地域連携クリティカルパスの整備ががん診療連携拠点病院の指定要件となる前であった。2012年3月現在，前立腺がん5種のクリティカルパスを運用しており，症例数は1,600例であった。今回われわれは2007年11月から2008年10月までの1年間に3種類の前立腺がんクリティカルパスが適応となった248例を対象に運用状況の調査とバリアンス解析を行い，クリティカルパスの妥当性について検討を行った。

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I　対象・方法

対象は2007年11月から2008年10月までの1年間に前立腺がん地域連携クリティカルパスを適用した248例である。地域連携クリティカルパスは3種類ありそれぞれの適応条件（**表1**）と症例数を以下に示す[3]。

PSA経過観察クリティカルパス：PSA高値（4.0ng/m*l*以上）で前立腺生検を施行し結果が陰性であった症例：110例，前立腺全摘術後経過観察クリティカルパス：限局性前立腺がんに対し前

表1　前立腺特異抗原（PSA）を用いた3種類の地域連携クリティカルパス

地域連携クリティカルパスの名称	対象患者	適応開始条件	アウトカムの設定	バリアンス発生時
PSA経過観察	PSA高値／生検陰性	PSA 4.0ng/ml以上，前立腺生検：陰性	PSA定期検査：生検時の1.4倍未満を確認	前回の生検時のPSA1.4倍以上⇒パス運用開始施設へ再紹介
前立腺全摘後	限局性前立腺癌／前立腺全摘除術後	PSA 0.2ng/ml未満，尿失禁の改善	PSA定期検査：PSA 0.2ng/ml未満を確認	PSA 0.2ng/ml以上⇒パス運用開始施設へ再紹介
内分泌療法	前立腺癌／内分泌療法	PSA 4.0ng/ml未満	PSA定期検査：PSA 2.0ng/ml未満を確認	PSA 2.0ng/ml以上⇒パス運用開始施設へ再紹介

表2　地域連携クリティカルパスバリアンスの35例の内訳

PSA値の上昇	9例　(4%)
連携医療機関での継続受診なし	23例　(9%)
●医療機関での継続受診あり（16例）	
●医療機関での継続受診なし（7例）	
●連絡とれず（1例）	
その他	3例　(1%)
合計	35例　(14%)

(%)：全症例（248例）に対する割合

立腺全摘除術を施行しPSAが低値である（0.2ng/ml未満）：69例，内分泌療法クリティカルパス：内分泌療法を開始しPSAが基準値（4.0ng/ml）未満まで低下し内分泌療法を継続していく：69例であった。連携医療機関での血清PSA値の測定間隔についてはPSA経過観察クリティカルパスの場合4～6ヵ月ごととし，前立腺全摘後および内分泌療法後クリティカルパスでは3ヵ月ごとと規定している[3]。地域連携クリティカルパスのアウトカムは**表1**のように設定した[3]。

千葉県がんセンター地域医療連携室が主だった連携医療機関13施設への患者の受診状況を調査し，地域連携クリティカルパスのバリアンス分析を行った。連携医療機関で受診状況を把握できていない患者については，地域医療連携室の担当者が患者へ直接電話し受診の有無や現在の通院状況などの聞き取り調査を行った。

Ⅱ　結　果

今回の1年間において新規治療総数に占めるクリティカルパス登録の割合は，PSA経過観察クリティカルパスでは，前立腺針生検334例中72例（22%），前立腺全摘後クリティカルパスでは，手術症例115例中14例（12%），内分泌療法クリティカルパスでは，新規治療開始88例中10例（11%）であった。それ以外は，2007年10月以前の症例の適応であった。

受診状況の調査の結果，クリティカルパス適用継続は213例（86%）であり，バリアンス発生が35例（14%）であった。バリアンスの内訳は，PSA値の上昇9例（4%），連携医療機関に継続受診なし23例（9%），その他3例（1%）であった（**表2**）。

連携医療機関に継続受診しなかった23例(9%)を検討すると，連携医以外の医療機関での継続あり16例（6%）（当センター再受診4例を含む），医療機関への受診なし7例（3%），連絡とれず1例（0.4%）であった。

医療機関への受診なし7例をクリティカルパス別にみると，PSA経過観察が5例で前立腺全摘後は2例であった。この7症例はいずれも検診を利用することでPSAの経過を自己管理していた。

クリティカルパス別にバリアンス例を検討すると，PSA経過観察が110例中22例（20%）と最も多く，次いで前立腺全摘後69例中9例（13%），内分泌療法69例中4例(6%)の順であった(**図1**)。

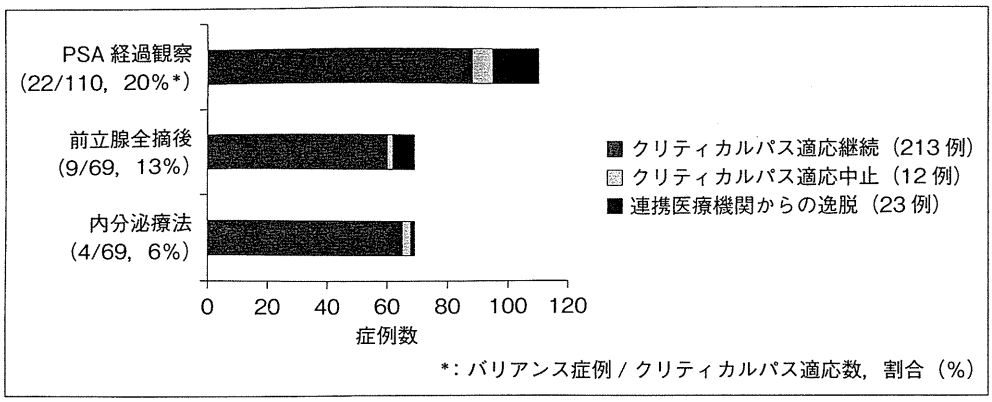

図1 地域連携クリティカルパス別のバリアンスの割合

Ⅲ 考 察

従来の地域連携では多くの場合，中核病院から地域医療機関（多くは開業医師）へ紹介された後は連携先の担当医師が判断し治療が行われてきた。医療レベルの高い中核病院で治療方針が決定した後，自宅近くの医療機関で治療を継続して受けられることは患者にとっての大きなメリットである。しかし紹介後の治療内容は担当医師の裁量に委ねられることが多く，再紹介のタイミングを逸すれば病状の悪化につながりかねず患者が不利益を被りかねない。また，地域医療を担う医師にとっても高リスク症例を担当することは大きなストレスとなる。特にがん患者の再紹介はがんの再発や進展を見逃すリスクを伴うため，良性疾患を中心に患者治療を行っている地域医療機関からあまり望まれない傾向にある。

地域医療機関に紹介される患者と連携先の担当医師双方のメリットとなる様に，われわれのクリティカルパスはアウトカムの設定すなわち再紹介の時期を明確に設定してある。再紹介の時期が明確になることで患者にがん診療の質と安心を保証するだけでなく，地域医療機関の担当医師にかかるストレスも軽減することができたと考えられる。ただし，がん診療の質を高く保っていくためには，バリアンス分析に基づくクリティカルパスの改善を図る必要がある。これまでに地域連携クリティカルパスの運用を開始したという報告は多くみられるが，十分なクリティカルパスの運用数があり，かつバリアンス分析も行った報告は少ない。今回われわれが行ったのは前立腺がんクリティカルパス3種類についての妥当性の検討とバリアンスの解析である。これまでのクリティカルパスにおけるバリアンスの収集方法は大きく3方式に分けられている。それぞれ，①ゲートウェイ方式：設定されたアウトカムが達成されなかった場合をバリアンスとして収集する方法，②センチネル方式：重要なアウトカム（クリニカルインディケーター）が達成されなかった場合のみをバリアンスとして収集する方法，③オールバリアンス方式：設定されたアウトカムだけでなく，すべての患者状態・医療ケア行為に対する異常をバリアンスとして収集する方法，である[4]。今回の検討では，ゲートウェイ方式をとりバリアンスの収集を行った。この収集方法によるバリアンスの発生は248例中35例（14%）であった。バリアンス35例の内訳はPSA経過観察クリティカルパスが最も多く同クリティカルパス適用例のうち20%，次に前立腺全摘後クリティカルパスの13%であった。内分泌療法クリティカルパスはバリアンス発生率が適用例のうち6%と低値だった。経過観察のみでなく治療を続ける必要があるクリティカルパスでは，継続して医療機関を受診する必要性があり，クリティカルパスの継続に関連すると考えられた。

今回の検討でクリティカルパス適用後に「連携医療機関を一度も受診していない」や「一度は受診したが継続的な受診をしていない」などの連携医療機関からの逸脱症例が23例（9%）みられた。これはわれわれのクリティカルパスが千葉県がんセンターへの定期的な受診を義務付ける循環式ではないための特有の現象と思われた。連携診療が継続されていくことが地域医療クリティカルパスにおいての重要なアウトカムであるため，今後は連携診療の継続の有無についてもバリアンスとして検出する必要があると考えられた。今回の検討

を踏まえて，これまでのアウトカムに「診療計画に沿って，定期的な検査が行える」を追加し，連携診療の継続の有無をバリアンスに加えて今後の分析を行っていく予定である。

連携から外れたものが23例（9%）あることの1つの原因としてクリティカルパスについて説明不足があげられる。外来診療での限られた診療時間内では，担当医師がクリティカルパスの運用についての説明を詳細に行い，且つ，患者側が今後の治療や経過観察がどのように行われていくのかを十分に理解を得ることは困難と考えられた。今回のバリアンス解析をもとに対策としてわれわれの施設では，患者の地域連携クリティカルパスへの理解と診療の継続を高める目的で「地域連携コーディネータ」を任命し泌尿器科外来へ配置している。専任の地域連携コーディネータが中心となり，患者オリエンテーション用パンフレットと地域連携の啓発リーフレットを作成し，これを用いて患者へ説明することで，オリエンテーションの質の均一化を図った。また，患者へ質の高い地域医療連携の提供をするために，地域連携コーディネータが外来担当看護師へのパスに関する教育を行っている。

がん治療後経過観察目的での地域連携クリティカルパス導入を試みる医療施設が多くなる中，実際には運用されている症例数が少ないため，その多くがバリアンス解析の報告まで至っていない。今回われわれは，地域連携クリティカルパス導入開始後の運用例248例のバリアンス解析を行った。今回の検討でがんの再発や連携診療の継続がアウトカムとなることが改めて認識された。われわれの地域連携クリティカルの質の向上を図るためには，今回のバリアンス解析を基にさらにクリティカルパスの設計を見直していくと同時に，患者支援の充実及びネットワークづくりの強化を図る必要があると考えられた。

クリティカルパスと医療コストの関係性については，現時点では以下の効果が考えられる。当センターでは千葉市以外の遠隔地から通院する場合が多いため，患者や付き添う家族が負担する交通費や通院にかかる時間が軽減できる。また，クリティカルパスの登録は平成24年3月まで1,600例である。これらの患者が1人あたりすべて3ヵ月に1度当センターに受診するとして単純計算で年間6,400回受診が必要である。年間55週とすると1日あたり23人の外来受診が増える。これだけの患者の受診を減らしていることは，外来の負担軽減に結びついていると思われる。

今後の問題点として，多くの症例が地域連携クリティカルパスの適応となることが予想されるため，運用数の増加に伴い，運用例すべてを連携の枠内で把握することが困難になることがあげられる。このため，患者状況の効率的な収集方法を開発する必要がある。今後，地域連携クリティカルパス導入開始後2年まではアンケート法によるバリアンスの解析を行い，その結果と今回の分析結果とを比較し，患者の通院状況をより簡便に把握する方法を検討開発する予定である。さらに今回の検討から個々の地域連携クリティカルパスの改定に取り組む予定である。

結　語

千葉県がんセンター泌尿器科では千葉県内の泌尿器科開業医を中心とした地域医療機関との連携を開始するにあたり，前立腺がんの治療や経過観察を目的とした地域連携クリティカルパスを作成導入している。運用開始1年を経過した時点で前立腺がんにおける3種類の地域連携クリティカルパスのバリアンス分析を行った結果，アウトカムの設定は良好だった。一方，バリアンス例の中には，診療連携から外れた症例が一定数みられており，地域連携クリティカルパスのアウトカム設定に診療連携の継続を追加することが今後の課題と思われた。

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Abstract

Variance Analysis of Regional Cooperation Critical Pathway for Prostate Cancer

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Beginning in November 2007, we at the Department of Urology of the Chiba Cancer Center developed critical pathways for urological cancer in association with regional private clinics of urologists, and we commenced regional medical cooperation. As of October 2011, we have employed 5 prostate cancer-related critical pathways on 1460 cases. We analyzed variance for 248 cases in which the three regional cooperation critical pathways about prostate cancer were used for 1 year until October 2008. We performed the analysis by surveying urologists at the cooperating medical institutions. The paths were followed on 213 cases (86%), but they were dropped with 35 cases (14%) "variance of the critical pathways." Based on these results, considering the outcome setting conditions, we thought that the current level of use of regional cooperation critical pathways was appropriate. However, since 9% of the cases "veered away from the paths," we thought that it would be necessary to add "continuous cooperative medical treatment" to future critical pathways outcomes.

key words：regional cooperation critical pathway, prostate cancer, variance

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TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial

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Summary

Background Treatments that confer survival benefit are needed in patients with heavily pretreated metastatic colorectal cancer. The aim of this trial was to investigate the efficacy and safety of TAS-102—a novel oral nucleoside antitumour agent.

Methods Between August 25, 2009, and April 12, 2010, we undertook a multicentre, double-blind, randomised, placebo-controlled phase 2 trial in Japan. Eligible patients were 20 years or older; had confirmed colorectal adenocarcinoma; had a treatment history of two or more regimens of standard chemotherapy; and were refractory or intolerant to fluoropyrimidine, irinotecan, and oxaliplatin. Patients had to be able to take oral drugs; have measurable lesions; have an Eastern Cooperative Oncology Group performance status of between 0 and 2; and have adequate bone-marrow, hepatic, and renal functions within 7 days of enrolment. Patients were randomly assigned (2:1) to either TAS-102 (35 mg/m² given orally twice a day in a 28-day cycle [2-week cycle of 5 days of treatment followed by a 2-day rest period, and then a 14-day rest period]) or placebo; all patients received best supportive care. Randomisation was done with minimisation methods, with performance status as the allocation factor. The randomisation sequence was generated with a validated computer system by an independent team from the trial sponsor. Investigators, patients, data analysts, and the trial sponsor were masked to treatment assignment. The primary endpoint was overall survival in the intention-to-treat population. Safety analyses were done in the per-protocol population. The study is in progress and is registered with Japan Pharmaceutical Information Center, number JapicCTI-090880.

Findings 112 patients allocated to TAS-102 and 57 allocated to placebo made up the intention-to-treat population. Median follow-up was 11·3 months (IQR 10·7–14·0). Median overall survival was 9·0 months (95% CI 7·3–11·3) in the TAS-102 group and 6·6 months (4·9–8·0) in the placebo group (hazard ratio for death 0·56, 80% CI 0·44–0·71, 95% CI 0·39–0·81; p=0·0011). 57 (50%) of 113 patients given TAS-102 in the safety population had neutropenia of grade 3 or 4, 32 (28%) leucopenia, and 19 (17%) anaemia. No patient given placebo had grade 3 or worse neutropenia or leucopenia; three (5%) of 57 had grade 3 or worse anaemia. Serious adverse events occurred in 21 (19%) patients in the TAS-102 group and in five (9%) in the placebo group. No treatment-related deaths occurred.

Interpretation TAS-102 has promising efficacy and a manageable safety profile in patients with metastatic colorectal cancer who are refractory or intolerant to standard chemotherapies.

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Introduction

Colorectal cancer accounts for about 10% of all cancer cases and is the fourth leading cause of cancer-related deaths worldwide.[1] Cytotoxic agents such as a fluoropyrimidine, irinotecan, and oxaliplatin, and antibodies such as bevacizumab (an anti-VEGF monoclonal antibody) and cetuximab and panitumumab (anti-EGFR monoclonal antibodies) significantly improve the survival of patients with unresectable metastatic colorectal cancer.[2–5] Although many patients have a good long-term performance status, a standard treatment for those who are refractory to or unable to tolerate these agents does not exist.

TAS-102 (Taiho Pharmaceutical, Tokyo, Japan) is a novel oral nucleoside antitumour agent consisting of α,α,α-trifluorothymidine (FTD) and 5-chloro-6-(2-iminopyrrolidin-1-yl) methyl-2,4 (1*H*,3*H*)-pyrimidinedione hydrochloride (TPI) at a molar ratio of 1:0·5. FTD is the active antitumour component of TAS-102: its monophosphate form inhibits thymidylate synthase and its triphosphate form is incorporated into DNA in tumour cells. The incorporation into DNA is known to have antitumour effects, because inhibition of thymidylate synthase caused by oral FTD rapidly disappears after the drug's elimination.[6] TPI is a potent inhibitor of thymidine phosphorylase, which is the enzyme that degrades FTD. After intravenous injection of FTD alone, sufficient concentrations have been recorded in plasma.[7] However, when monkeys are given oral FTD alone, it is rapidly degraded to its inactive

form in the intestines and liver (first-pass effect). Therefore, TPI is necessary to maintain adequate plasma concentrations of FTD that has been taken orally.[8]

Preclinical studies[9,10] have shown that TAS-102 exerts an antitumour effect against cancer cells irrespective of their sensitivity to fluoropyrimidines. TAS-102 has a mechanism of action different from that of other antitumour agents such as a fluoropyrimidine, irinotecan, and oxaliplatin. As a result, TAS-102 is expected to be effective against tumours refractory to the various antitumour agents available.

The results of several independent phase 1 clinical trials[11–13] of patients with solid tumours in the USA showed that the optimum dosage of TAS-102 was a 28-day cycle: a 2-week cycle of 5 days of treatment followed by a 2-day rest period, and then a 14-day rest period. The maximum tolerated dose was 25 mg/m² given orally twice daily to patients with heavily pretreated breast cancer.[14]

Subsequently, a phase 1 clinical trial[15] was done in Japan; the recommended dose was 35 mg/m² twice daily given orally, with the same treatment cycle. 21 patients were enrolled in the Japanese phase 1 study,[15] 18 of whom had colorectal cancer. Clinical benefit was achieved in 11 patients, including one with a partial response; eight were able to continue treatment for 12 weeks. These results suggested that TAS-102 could further improve the outcomes of patients with unresectable metastatic colorectal cancer who have already received conventional chemotherapy with a fluoropyrimidine, irinotecan, and oxaliplatin. Thus, we further investigated the efficacy and safety of TAS-102.

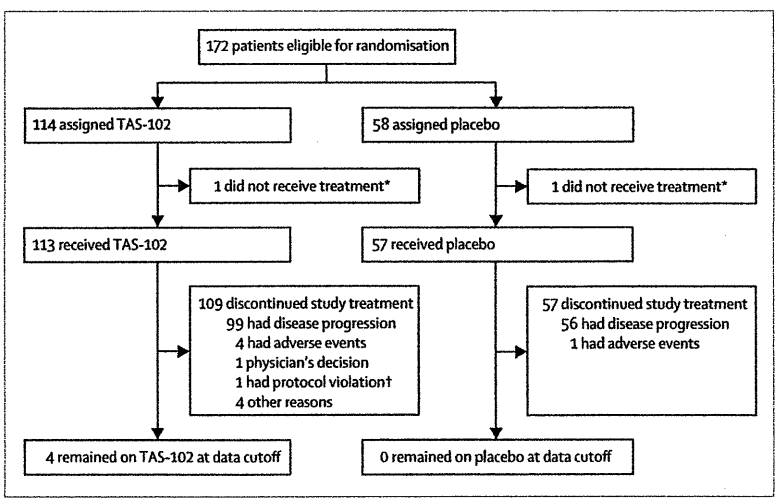

Figure 1: **Trial profile**

*One patient was randomly allocated to TAS-102 did not receive treatment because of aggravation of a rash related to previous chemotherapy and one patient allocated to placebo did not receive treatment because of occurrence of pulmonary thromboembolism; these patients were excluded from the efficacy and safety populations. †One patient received TAS-102 but was concomitantly taking a prohibited treatment, so was excluded from the efficacy population, but included in the safety population.

Methods

Study design and participants

Between Aug 25, 2009, and April 12, 2010, we undertook a multicentre, double-blind, randomised, placebo-controlled phase 2 trial of TAS-102 in Japan. Eligible patients were 20 years or older; had histologically or cytologically confirmed unresectable metastatic colorectal adenocarcinoma; had a previous treatment history of two or more regimens of standard chemotherapy; and were refractory or intolerant to a fluoropyrimidine, irinotecan, and oxaliplatin. Patients had to be able to take oral drugs; and to have measurable lesions as per the Response Evaluation Criteria In Solid Tumors (RECIST; version 1.0)[16] and an Eastern Cooperative Oncology Group (ECOG) performance status of between 0 and 2. Adequate bone-marrow, hepatic, and renal functions were established by tests within the 7 days before enrolment. Patients could have no serious comorbidities.

Previous treatments were discussed by the investigators in charge and study monitors before enrolment to confirm eligibility—ie, whether progression of disease as documented in medical records could be reasonably interpreted as refractory, and whether discontinuation due to unacceptable toxic effects could be reasonably interpreted as intolerance. Whether patients of doubtful eligibility could be enrolled was assessed by the steering committee (AO, TD, IH, and HB) at a central review meeting.

The study was done in accordance with the Declaration of Helsinki and the Japanese Good Clinical Practice guideline. The protocol was approved by the institutional review boards of participating hospitals. Written informed consent was obtained from all patients.

Randomisation and masking

Patients were randomly assigned in a 2:1 ratio to either TAS-102 plus best supportive care or placebo plus best supportive care through central registration. Randomisation was done with minimisation methods, with baseline ECOG performance status (0 *vs* 1 or 2) as the allocation factor. The randomisation sequence was generated by an independent team from the trial sponsor who used a validated computer system. Assignment of patients was initiated via fax. The investigators, patients, data analysts, and the trial sponsor were masked to the randomisation sequence and treatment assignment.

Procedures

A dose of 35 mg/m² TAS-102 was taken orally twice a day after meals (ie, 70 mg/m² per day). Two tablets (15 mg and 20 mg) were used to achieve the correct dose. TAS-102 or placebo was taken in a 28-day cycle: a 2-week cycle of 5 days of treatment followed by a 2-day rest period, and then a 14-day rest period. Placebo was matched to TAS-102 tablets for taste, colour, and size, and contained lactose, partly pregelatinised starch, stearic acid, hydroxypropyl methyl cellulose, polyethylene glycol, and