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Clinical Medicine Insights: Case Reports

Personalization of Chemotherapy for Metastatic Pancreatic Cancer

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ABSTRACT: Erlotinib is an approved drug for the treatment of advanced pancreatic cancer; however, its survival benefit is small and its cost is high, and the decision to use the drug may often be personalized according to the patient's background. A 72-year-old Asian man in good general condition chose gemcitabine monotherapy over combination therapy with gemcitabine plus erlotinib because the survival benefit of the latter was small. The cost of the drug did not appear to affect this decision. This report details the process of decision making with respect to whether a patient receives targeted therapy, and suggests that the use of molecular-targeted drugs must be personalized from many perspectives, including the patient's social situation.

KEYWORDS: drug cost, molecular-targeted drug, pancreatic cancer

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Introduction

Gemcitabine has been the standard drug for the treatment of pancreatic cancer as a first-line therapy since 1997.[1] In the US, erlotinib was approved for the treatment of advanced pancreatic cancer in 2005 based on a Phase III trial that indicated statistically superior overall survival for gemcitabine plus erlotinib compared to gemcitabine alone.[2] In the Phase III study, erlotinib plus gemcitabine was associated with significantly longer progression-free survival than gemcitabine alone (median, 3.75 vs. 3.55 months). Objective response rates were not significantly different between the arms (8.6% vs. 8.0%); however, a higher incidence of some adverse events was observed with erlotinib plus gemcitabine.[2] In Japan, erlotinib was approved in 2011. However, 8.5% of Japanese patients subsequently developed interstitial pneumonia,[3] which can be fatal, and the survival benefit, which was only 0.33 months improvement in overall survival, was small.[2] Thus, the overall risk–benefit assessment of this drug remains controversial. In addition, erlotinib is relatively expensive, and thus the increase in health care costs is also an issue. In the review report[4] of the Pharmaceuticals and Medical Devices Agency (PMDA), the reviewing authority for drug approval in Japan, specialists discussed the risks and benefits of this drug, and their evaluation was controversial. Given the risk of severe adverse effects, such as interstitial pneumonia, some specialists claimed that the survival benefit of this drug is too small. The benefits of erlotinib are not sufficiently high to recommend it strongly to patients. Thus, decisions related to its use may often be personalized according to the patient's background, including factors such as economic or social conditions. However, no previous reports have investigated the decision-making processes used by patients and physicians.

The case of a patient in good general condition who chose gemcitabine monotherapy after refusing combination therapy with gemcitabine plus erlotinib is presented. Based on this case, factors in addition to the patient's physical condition that affected the choice of treatment were investigated. To the best of our knowledge, this is the first report to focus on the

decision-making process of a patient while taking their social situation into account.

Case Presentation

A 72-year-old Asian man with a past history of cerebral infarction, hypertension, diabetes mellitus, and hepatitis B visited a hospital for treatment of prostate cancer (stage I). He was found to have jaundice on physical examination, and obstructive jaundice due to cancer of the head of the pancreas was diagnosed. Surgery after endoscopic retrograde biliary drainage revealed No. 16 lymph node metastasis. Thus, his pancreatic cancer was judged to be unresectable. After choledochojejunostomy and gastrojejunostomy, chemotherapy was planned. With respect to the patient's social situation, he was retired and lived alone with his wife. His hobby was drawing pictures, which he did every day along with his wife. The cost of the treatment did not present a financial burden. Written, informed consent to report his information was obtained in accordance with the requirements of the Institutional Review Board in Yamagata Prefectural Central Hospital.

It was explained to both the patient and his wife that he had unresectable and incurable cancer. Several treatment options were suggested, including gemcitabine plus erlotinib, gemcitabine monotherapy, and S-1 (tegafur, gimeracil, and oteracil potassium in a molar ratio of 1:0.4:1). Brochures detailing the adverse events and the efficacy of these chemotherapies were also provided, along with information concerning the cost of erlotinib and assistance available for high-cost medical care through the public health insurance system. This information had also been provided by caseworkers in the hospital, while information about the support system for high-cost medical care had been provided at the local City Hall. He was also informed that he could be treated in a nearby hospital. Gemcitabine plus erlotinib was recommended because this regimen showed evidence of longer overall survival of about 2 weeks compared to gemcitabine alone, even though the risk of interstitial pneumonia was higher in Japanese patients. He did not have the symptoms of cerebral infarction, and his diabetes was controlled with oral medicine. He had no liver dysfunction and HBV-DNA was negative; entecavir was necessary for prevention, according to the guidelines. Because his performance status was 1, he was considered able to tolerate combination therapy using gemcitabine plus erlotinib. The patient and his wife chose gemcitabine monotherapy, primarily because the prolongation of survival with gemcitabine plus erlotinib was only expected to be about 2 weeks. He lived for drawing and did not wish to suffer any debilitating side effects; therefore, he rejected the combination therapy.

Gemcitabine monotherapy was started with entecavir for hepatitis B virus. The patient received gemcitabine monotherapy treatment biweekly because of neutropenia. The only side effect was grade 1 fatigue, and his performance status was 1 during chemotherapy. Three months after the start of the chemotherapy, he was found to have small nodules in both lungs. Because these nodules were very small, it was uncertain whether they were lung metastases or inflammatory nodules. The best response to treatment was stable disease. He remained at stable disease for 1 year, and none of the nodules increased in size. The patient received gemcitabine monotherapy for 14 months; however, disease progression was seen. He then received chemotherapy with S-1 for 3 months, but new bone metastases developed. Thereafter, he received palliative treatment. No change was observed in his prostate cancer during the chemotherapy. Because of cancer-related pain from the bone metastases, he received radiation therapy to the vertebra. He was then transferred to a hospital near his home. Two years after diagnosis, the patient died at home.

Discussion

To the best of our knowledge, this is the first known report of the decision-making process of a patient eligible to receive targeted therapy. Although this patient's performance status was good, he did not choose targeted therapy.

Physicians generally recommend chemotherapy regimens based on the evidence and the patient's general condition. Although decision making about treatment in clinical practice is usually led by physicians, the number of cases in which patients take the initiative in decision making is increasing. Patients' decisions are often influenced by factors such as alopecia, costs, or survival benefit.[5,6] Even with the same type of cancer, staging, age, or sex, patients' treatment choices vary based on the factors such as income and family structure. Profiles of adverse events in targeted therapies differ from those of cytotoxic therapies. Some targeted drugs have specific adverse effects; for example, erlotinib and cetuximab are associated with skin toxicity, while trastuzumab is associated with heart failure. Moreover, drug costs of targeted therapies are obviously higher than those of cytotoxic therapies (Table 1). In addition, some patients place quality of life above survival benefit. This case report revealed that the treatment strategy, that is, the decision either to use or not to use targeted therapy, must be personalized.

The high cost of erlotinib therapy is also problematic.[7] Nevertheless, the cost of the drugs did not appear to affect this patient's choice of treatment. In general, Japan's health insurance system is financed through social insurance, similar to Germany or the Netherlands. In this system, patients pay a fixed proportion, which is limited, of the total treatment cost. Meanwhile, the health insurance system of the United Kingdom is financed through taxes and thus requires no payment from the patient. On the other hand, the system in the United States is based on private insurance, and thus medical costs vary based on the insurance company and the terms of the contract. Expensive drugs are available at a fixed cost in Japan because of National Health Insurance and assistance for high-cost medical care that it provides. Cost is not so important for patients aged 70 years or over, who pay reduced rates for medical care; however, patients under 70 years of age may be faced with medical bills up to 80,000 yen (825 US dollars)

Table 1. Pros and cons of both regimens.

	GEMCITABINE+ERLOTINIB	GEMCITABINE MONOTHERAPY
Pros	Prolonged overall survival compared with gemcitabin monotherapy	Less of toxicity compared with gemcitabine plus erlotinib therapy
Cons	Survival benefit is small	Less of survival benefit compared with gemcitabine
	Drug cost is high	
	Increase of toxocity (skin toxicity, interstitial pneumonia etc.)	
Drug cost in this case per month*	270,472 yen (2788 US dollars)	54,982 yen (567 US dollars)
Medical bill that he really pays per month in an outpatient clinic#	44,400 yen (457 US dollars)	44,400 yen (457 US dollars)

Notes: The cost of gemcitabine (1 g) set by the National Health Insurance is 14,815 yen (153 US dollars; $1 = 97 yen). *In this case, gemcitabine was administered at 1000 mg/m^2 (1800 mg/body) biweekly. #the patient's drugs were covered by the public health insurance system.

per month, which is the limit set for monthly expenditures by the social insurance system. If patients are unable to work due to disease, medical bills become a major problem. However, cost is not a factor discussed during the drug approval review process of the PMDA. In the review report of erlotinib, the risk–benefit assessment by specialists was controversial. As the patient's cost burden is fixed, it is easy for patients and physicians to use high cost molecular-targeted drugs in countries with a universal insurance system; however, if these drugs are used, the national cost of medical care consequently increases. Therefore, the use of expensive molecular-targeted drugs accelerates the increase in cost of medical care while only providing a small benefit to patients.

In summary, the factors that affect the choice of molecular-targeted drugs were discussed based on the present case. Use of molecular-targeted drugs should be personalized. To facilitate optimal decision making for patients, close communication based on the patient's background, including socioeconomic factors, comorbidities, and decision-making preferences is important. A survey of molecular-targeted drug usage among physicians is currently being conducted, and a questionnaire survey of patients on the use of molecular-targeted drugs is planned for the future.

Author Contributions

Conceived the concept: YS, HN. Analyzed the data: YS, HN. Wrote the first draft of the manuscript: YS, HN. Contributed to the writing of the manuscript: YS, HN, SS, TF, HS, NS, TY. Agree with manuscript results and conclusions: YS, HN, SS, TF, HS, NS, TY. Jointly developed the structure and arguments for the paper: YS, HN, SS, TF, HS, NS, TY. Made critical revisions and approved final version: YS, HN. All authors reviewed and approved of the final manuscript.

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