Department of Hospital Pharmaceutics[1], School of Pharmacy, Showa University; Department of Date Science/Pharmacy[2], National Cancer Center Hospital East; Department of Pharmacy[3], The Cancer Institute Hospital of Japanese Foundation for Cancer Research; Department of Nursing[4], School of Nursing and Rehabilitation Sciences, Showa University; Division of Applied Pharmaceutical Education and Research[5], Hoshi University, Tokyo, Japan

Cost-effectiveness of primary prophylaxis of febrile neutropenia with pegfilgrastim in docetaxel, cisplatin and 5-fluorouracil therapy for esophageal cancer

T. Ichimura[1], H. Nomura[2], H. Shimizu[3,4] Y. Machida[5], K. Suzuki[5,*]

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**Corresponding author: Kenichi Suzuki, Division of Applied Pharmaceutical Education and Research, Hoshi University, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142-8501, Japan*
kenichi-suzuki@hoshi.ac.jp

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Objective: The efficacy of docetaxel, cisplatin, and 5-fluorouracil (DCF) therapy in treating esophageal cancer has been reported. However, febrile neutropenia (FN) is a potentially serious adverse event of DCF therapy with an incidence of 10 to 40%. Pegfilgrastim, a granulocyte colony-stimulating factor (G-CSF), has been shown to have a primary prophylactic role in FN. However, it has been suggested that excessive use of expensive G-CSF should be avoided. Therefore, we performed a cost-utility analysis of primary prophylaxis with pegfilgrastim. *Design*: Cost-effectiveness analysis using decision tree modelling. *Methods*: We used a decision tree analysis model based on the report of primary prophylaxis with pegfilgrastim. Based on a previous study, the FN incidence rate was set at 40.0% (95% confidence interval (CI): 11.9–68.1) for the pegfilgrastim group and 43.5% (95%CI: 21.6–65.4) for the no pegfilgrastim group. The FN treatment cost was US$726.63, and the duration of FN was 3.65±1.20 days. The utility value of patients who received DCF therapy was 0.643, and the change in utility value at FN onset was -0.15. Expected cost, quality-adjusted life year (QALY), and incremental cost-effectiveness ratio (ICER) were calculated, and cost-utility analysis was performed. *Results*: The ICER of pegfilgrastim was 184,976.75 USD/QALY. As a result of sensitivity analysis, the utility of FN had the greatest impact on the cost-effectiveness analysis, followed by the drug cost of pegfilgrastim. *Conclusion*: Primary prophylaxis of FN with pegfilgrastim might not be cost-effectiveness. In determining whether to administer pegfilgrastim it is necessary to consider patient factors, not just the incidence of FN.

1. Introduction

Standard therapies for unresectable advanced or recurrent esophageal cancer are 5-fluorouracil and cisplatin (FP) therapy and docetaxel, cisplatin, and 5-fluorouracil (DCF) therapy, which shows a high response rate (67–81%) (Noronha et al. 2014; Osaka et al. 2011; Takahashi et al. 2010; Yamasaki et al. 2011). The utility of DCF therapy has also been reported in preoperative adjuvant chemotherapy (Akiyama et al. 2018; Miyata et al. 2017; Satake et al. 2016; Yamashita et al. 2017). One of the serious adverse effects of DCF therapy is febrile neutropenia (FN). The incidence of FN in DCF therapy has been reported to be 10 to 40% (Akiyama et al. 2018; Miyata et al. 2017; Takahashi et al. 2010; Takahashi et al. 2017; Yamasaki et al. 2011; Yamashita et al. 2017) and the administration of granulocyte colony-stimulating factor (G-CSF) to treated patients is recommended. Pegfilgrastim is a PEGylated form of G-CSF with a significantly prolonged elimination half-life. It has been shown to be a primary prophylactic for FN (Yoshida et al. 2018), as the frequency of FN in a pegfilgrastim group was significantly lower than that in a control group. Because of the high risk of death from FN, primary prophylaxis with G-CSF is recommended where FN incidence is ≥20% (Aapro et al. 2011; Crawford et al. 2017; Klastersky et al. 2016; Smith et al. 2015). Primary prophylaxis with pegfilgrastim has been assessed in clinical trials of patients with breast cancer (Vogel et al. 2005) and small cell lung cancer (Timmer-Bonte et al. 2006). However, the threshold setting of ñ20% for the incidence of FN is derived mainly from cost-effectiveness analysis in the United States (Lyman et al. 1998). This selection process needs to be verified in Japan, where the universal health care system differs. The price of G-CSF is high. In Japan, pegfilgrastim costs 996.56 USD (108,635 JPY) per injection, as of 2019.

In Japan, all citizens subscribe to the universal health care system (Ikegami and Campbell 1995). The patient pays a portion of the medical costs associated with the treatment, such as laboratory costs, hospitalization costs, and drug costs. Public agencies pay the rest. Drug prices are fixed and determined by the Japanese government based on the price of similar drugs. If there is no similar drug, the price is determined by development and production costs. The universal health care system has been used not only Japan but also in many other countries.

Administration of pegfilgrastim can prevent serious adverse events. It is also advantageous because it reduces the burden of attending hospital on patients and the cost of medical staff (Pfeil et al. 2015). In Japan, pegfilgrastim is more expensive than filgrastim, which requires daily administration. However, there is no difference in the incidence of FN in Japanese validation studies. It is necessary to analyze patient background factors in primary prophylaxis with pegfilgrastim. It has also been reported that the primary prophylaxis with G-CSF does not reduce mortality (Lyman et al. 2013), infectious (Lyman et al. 2002) and disease-related deaths (Smith et al. 2015). Therefore, the cost-effectiveness of administering G-CSF is unclear. It has been suggested that excessive use of

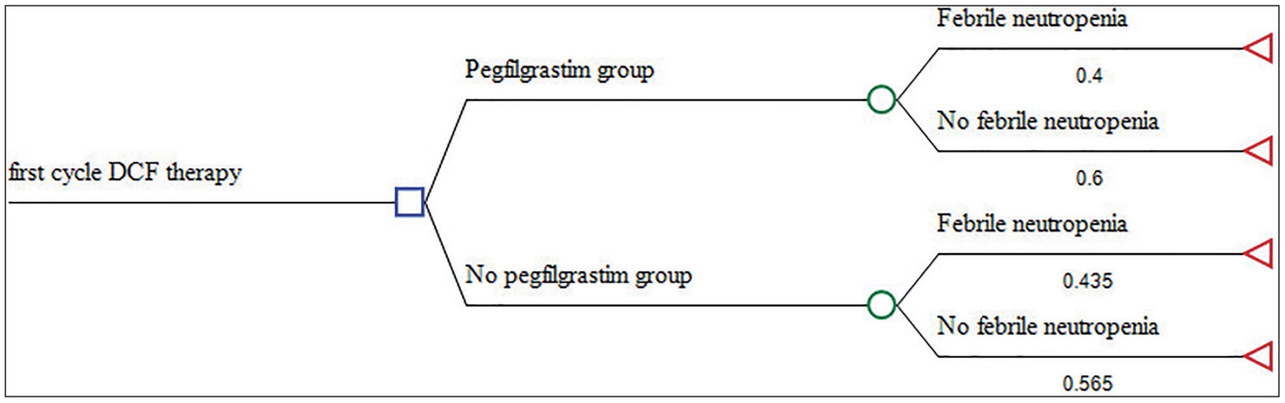

Fig. 1: Decision tree analysis model. Abbreviations: DCF; docetaxel, cisplatin, and 5-fluorouracil therapy.

expensive G-CSF should be avoided (Smith et al. 2015). Thus, it is necessary to investigate whether pegfilgrastim should be used uniformly as a primary prophylactic.

We focused on DCF therapy for esophageal cancer patients at a high risk of FN. The purpose of this study was to clarify whether pegfilgrastim should be administered as a primary prophylactic of FN. Using a decision tree analysis model, we analyzed the cost-utility of pegfilgrastim.

2. Investigations and results

2.1. Setting of decision tree model

We used the parameters of reports that focused on the prophylactic effect of pegfilgrastim in DCF therapy combining docetaxel (70 mg/m^2), cisplatin (75 mg/m^2), and 5-fluorouracil (700 mg/m^2) (Takahashi et al. 2017). Patients who received DCF therapy for esophageal cancer were included. There were 15 patients in the pegfilgrastim group and 23 patients in the no pegfilgrastim group. Pegfilgrastim was administered on day 6 to 2 patients and day 7 to 13 patients. The patient backgrounds between the groups were well balanced. Then, a decision tree analysis model was constructed for cost-utility analysis (Fig. 1).

The reported effective dose of DCF therapy is docetaxel: 70–75 mg/m^2, cisplatin: 70–75 mg/m^2, and 5-fluorouracil: 700–750 mg/m^2 for unresectable or advanced recurrent esophageal cancer and resectable esophageal cancer.

FN incidence rate is 20% or more.

We compared primary prophylaxis of FN with pegfilgrastim at the first administration of cancer chemotherapy to non-administration of pegfilgrastim. The pegfilgrastim group received a single dose of pegfilgrastim 3.6 mg upon completion of the first cycle of DCF therapy. The pegfilgrastim non-administration group (no pegfilgrastim group) received no primary prophylaxis upon completion of the first cycle DCF therapy. At the first selection point, either the pegfilgrastim group or the no pegfilgrastim group was selected. At the next point, we decided to proceed to each scenario depending on whether or not FN occurred. The time horizon was 28 days (one cycle of treatment); thus, no discount was given.

2.2. Evaluation methods

2.2.1. Definition of FN

FN was defined according to the following: (Crawford et al. 2017) Neutrophil count <500/μL (or <1000/μL and predicted to decrease to <500/μL within 48 hours).

Fever with an axillary temperature of 37.5 °C or higher, or oral temperature of 38.0 °C.

2.2.2. Cost and duration of FN treatment

The currency conversion rate was set at 1 US dollars (USD) = 109.1 Japanese yen (JPY) = using the exchange rate reported by the Organization for Economic Cooperation and Development (OECD) 2019. Based on a previous study (Sugimoto et al. 2018), we defined FN treatment cost as 726.63 USD (489.37–963.89) and the duration of FN as 3.65 (2.45–4.85) (Table).

In this previous study (Lyman et al. 2002), patients aged 65 and older with non-Hodgkin's lymphoma who received initial cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) therapy were included. Primary prophylactic administration of pegfilgrastim was performed and the change in utility value from the baseline to the onset of FN was -0.15 (Lathia et al. 2013). FN

Table: Parameters entered in the decision tree analysis model

Parameter	Value	Lower limit	Upper limit	Reference
Drug costs of pegfilgrastim (USD)	996.56	697.6	1295.53	Japanese National Health Insurance Drug Price Standard listed in 2019.
Treatment costs of febrile neutropenia (USD)	726.63	489.37	963.89	J Pharm Health Care Sci. 2018, 44, 441-448. (21)
The duration of FN	3.65	2.45	4.85	J Pharm Health Care Sci. 2018, 44, 441-448. (21)
Risk of febrile neutropenia in pegfilgrastim group (%)	40.0	11.9	68.1	J Pharm Health Care Sci. 2017, 43, 336-343. (9)
Risk of febrile neutropenia in no pegfilgrastim group (%)	43.5	21.6	65.4	J Pharm Health Care Sci. 2017, 43, 336-343. (9)
Utility value of esophageal cancer patients	0.643			J Clin Oncol. 2007, 25, 3210-3216. (22)
Utility value of febrile neutropenia	-0.15	-0.05	-0.25	J Natl Cancer Inst. 2013, 105, 1078-1085.(23)
Time horizon (days)	28			J Pharm Health Care Sci. 2017, 43, 336-343. (9)

Exchange rate, 1 USD = 109.01 JPY, based on the Organization for Economic Cooperation and Development (OECD) 2019.

treatment costs included hospital charges, drug costs, hematology tests, biochemical tests, bacterial cultures, and imaging tests, whereas costs not related to FN were excluded. The data on FN in patients receiving CHOP therapy for malignant lymphoma were used because the duration of FN and the cost of treatment were not clear when primary prophylaxis with pegfilgrastim was used in DCF therapy. This parameter was used because prophylaxis od FN in patients with malignant lymphoma has been reported to be the most expensive; thus, it was selected as it presents the worst case cost scenario (Dulisse et al. 2013).

2.4. Cost-utility analysis

The ICER associated with the administration of pegfilgrastim calculated from various parameters was 184,976.75 USD. This was more expensive than the threshold of 50,000 USD/QALY.

2.5. Sensitivity analysis

The effect of each parameter change on ICER was confirmed. The results of the 1-way sensitivity analysis are presented in a tornado diagram (Fig. 2). The utility of FN had the greatest impact on the

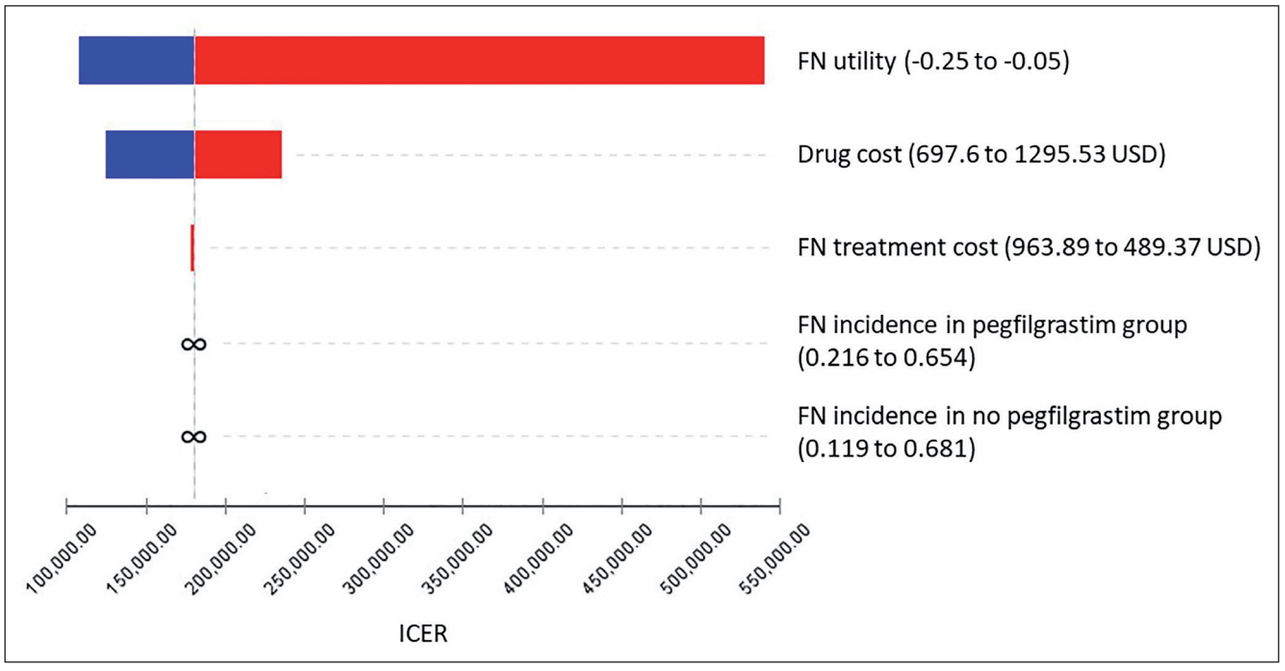

Fig. 2: Tornado diagram for 1-way cost-effectiveness sensitivity analysis. Abbreviations: FN; febrile neutropenia, ICER; incremental cost-effectiveness ratio.

DCF therapy requires the patient to be hydrated while receiving cisplatin to prevent nephrotoxicity and it is necessary to administer 5-fluorouracil for 5 consecutive days. Therefore, both groups were hospitalized.

2.2.3. Utility value

The utility value of patients receiving DCF therapy was set to 0.643 based on a previous study (Table) (Sugimoto et al. 2018). In this previous study, DCF therapy combining docetaxel (75 mg/m^2), cisplatin (75 mg/m^2), and 5-fluorouracil (750 mg/m^2) was administered to patients with esophageal cancer. The quality of life measurement method was EuroQol-5 Dimensions. The utility value before treatment was 0.787 and that after one course was 0.643. The change in the utility value at the onset of FN was set to -0.15 (95% confidence interval (CI): -0.05 to -0.25) based on a previous study (Table) (Lathia et al. 2013).

2.2.4. Transition probability

Based on a previous study (Lyman et al. 2002), the FN incidence rate was set at 40.0% (95%CI: 11.9–68.1) for the pegfilgrastim group and 43.5% (95%CI: 21.6–65.4) for the no pegfilgrastim group (Table).

2.3. Parameters entered in the decision tree analysis model

The parameters entered in the decision tree analysis model and the setting basis are shown (Table).

cost-effectiveness analysis, followed by the drug cost of pegfilgrastim. However, the influence of FN incidence was negligible. The parameters were considered to be uncertain based on the results of sensitivity analysis. Although the utility of FN is uncertain, pegfilgrastim has a certain cost; thus, we conducted a 1-way sensitivity analysis on the drug cost of pegfilgrastim. When the drug cost of pegfilgrastim was 290.4 USD, the willingness to pay threshold (50,000) USD was met (Fig. 3). Probabilistic sensitivity analysis was not performed owing to uncertainty.

3. Discussion

In this study, we examined the cost-utility of pegfilgrastim treatment in patients receiving DCF therapy for esophageal cancer. The ICER of pegfilgrastim treatment for primary prophylaxis in patients receiving DCF therapy for esophageal cancer was 184,976.75 USD, which exceeded the threshold value of 50,000 USD/QALY in cost-utility analysis. However, the parameters were considered to be uncertain based on the results of sensitivity analysis, and probabilistic sensitivity analysis was not performed owing to uncertainty. But, this result suggests that pegfilgrastim, as a primary prophylactic of FN in patients receiving DCF therapy for esophageal cancer might not be cost-effectiveness. And, reducing the drug cost of pegfilgrastim to 290.4 USD, which is 29.1% of the cost of pegfilgrastim in Japan, could be cost-effective. It has been shown in many fields that using biosimilars can reduce drug costs and result in other benefits. A pegfilgrastim biosimilar might be launched in Japan in the future but it may not be cost-effective unless the cost is reduced to 29.1% of the current price. Cost-ef-

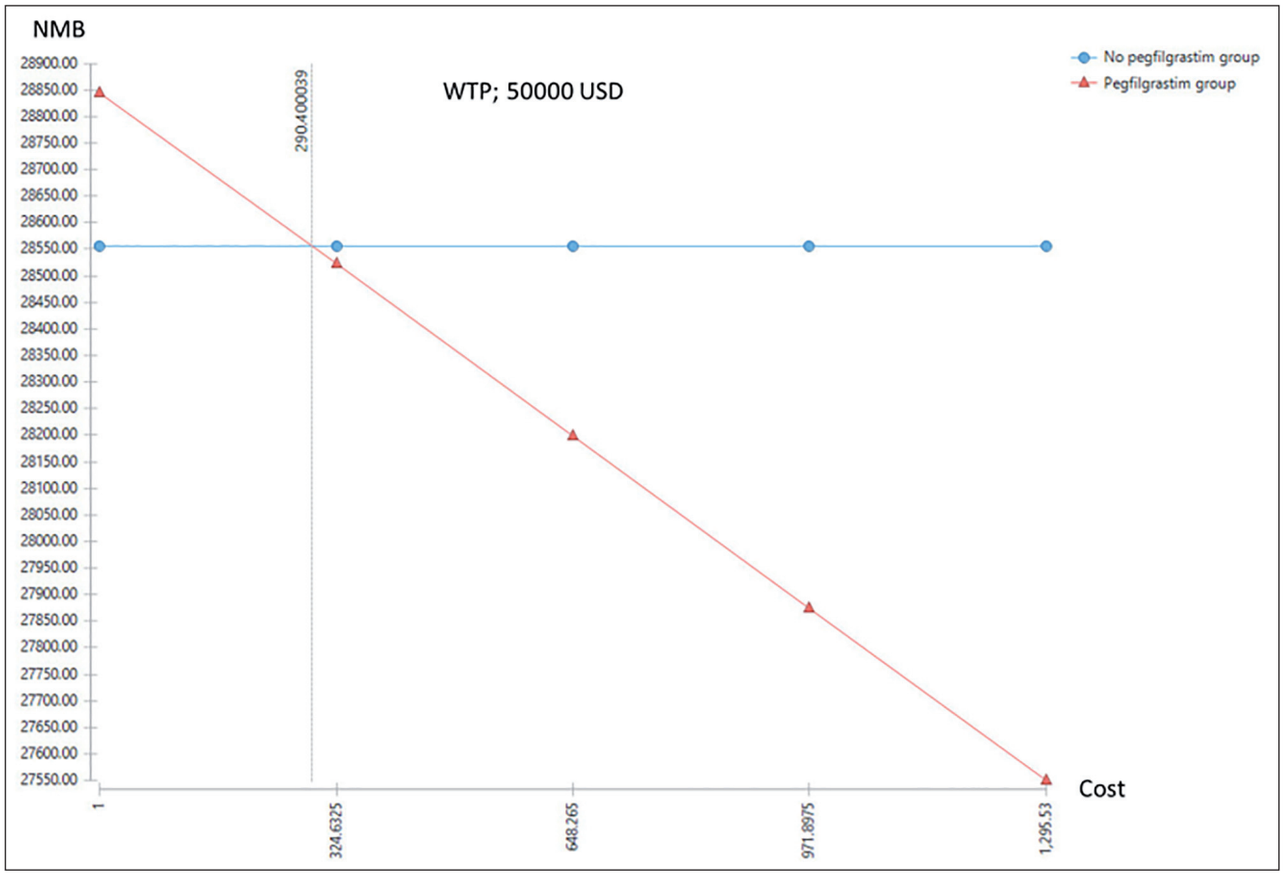

Fig. 3: One-way sensitivity analysis of pegfilgrastim drug cost. Abbreviations: NMB; Net monetary benefit, WTP; willingness to pay.

fectiveness of pegfilgrastim should be discussed in countries with universal health care system similar to Japan.

The main reason for not cost-effectiveness of pegfilgrastim was the low primary prophylactic effect of pegfilgrastim in patients receiving DCF therapy for esophageal cancer. A previous study showed that the FN incidence rate in the pegfilgrastim-treated group is 40%, whereas that in the no pegfilgrastim group is 43.5% (Sugimoto et al. 2018). The incidence of FN with DCF therapy for esophageal cancer is more than 20%, as with CHOP therapy for blood cancer patients (Morrison et al. 2001), docetaxel therapy for breast cancer patients (Vogel et al. 2005), and treatment for small cell lung cancer patients (Timmer-Bonte et al. 2006). In all of these situations, the incidence of FN is high. Possible reasons for the lack of significant reduction in the incidence of FN reported in the previous study (Sugimoto et al. 2018) are as follows:

1. Pegfilgrastim administration is on day 7 or later; thus, administration timing may be different among patients.
2. Unlike the group of breast cancer patients with good performance status who can be treated as outpatients (Vogel et al. 2005), DCF therapy is a regimen requiring inpatient treatment.
3. The purpose of treatment differs between preoperative adjuvant chemotherapy and treatment for unresectable or advanced recurrent cancer for the purpose of prolonging life.
4. Different patient backgrounds.

Our cost-effectiveness analysis revealed that the decision to undergo primary prophylactic treatment with pegfilgrastim should not be determined based on FN incidence alone. Indeed, the use of pegfilgrastim in DCF therapy is sometimes recommended. However, the patient's condition and the purpose of chemotherapy should be considered. For example, preoperative DCF therapy for esophageal cancer has been shown to be safe in phase II study without the prophylactic administration of G-CSF (Hara et al. 2013). In addition, if DCF therapy cannot be selected owing to a poor condition, other options, such as FP, should be considered instead of DCF therapy with pegfilgrastim. Thus, it is necessary to evaluate the patient's background, such as age (65 years and over), performance status, renal and hepatic function, and treatment history (Smith et al. 2015). Previous studies of preoperative DCF therapy for patients with esophageal cancer have identified age and solitude as risk factors for FN (Nomura et al. 2020). Therefore, it is important to investigate the mechanism of FN development in detail, find the optimal G-CSF administration method according to each patient's background, and elucidate the optimal timing of drug administration. Our results warn against the use of G-CSF as a primary prophylactic at least all of esophageal cancer patients in DCF therapy.

The limitation of this study is that several prior studies were used as parameters for cost-utility analysis, such as regarding utility value and FN incidence. Therefore, the background of esophageal cancer patients receiving DCF therapy may be different. In this study, the FN incidence rate was 20% or more, and primary prophylaxis with pegfilgrastim was compared with no pegfilgrastim in the first round of cancer chemotherapy. The dose of DCF therapy used as a parameter in previous studies was docetaxel: 70 mg/m^2, cisplatin: 75 mg/m^2, and 5-fluorouracil: 700 mg/m^2. However, the dose of DCF therapy reported to be effective range in values (70–75, 70–75, and 700–750 mg/m^2 for docetaxel, cisplatin, and 5-fluorouracil, respectively); thus, the dose used in practice varies. Apart from the patient background, differences in regimen doses may have led to an underestimation of the incidence of FN and the effect of pegfilgrastim. In this study, we used QALY, which is evaluated in 1 year, as a parameter of cost-utility analysis. However, as we evaluated a 28-day course of DCF therapy for preoperative patients, the effects of pegfilgrastim may be greater than estimated. Additionally, the time loss owing to serious adverse events in patients may differ between simulation models and the real-world. Therefore, further studies are needed to fully clarify the cost-effectiveness of primary prophylaxis with pegfilgrastim in patients receiving DCF therapy

for esophageal cancer. Firstly, patients receiving DCF therapy could be divided into two groups, receiving primary prophylaxis with G-CSF and not receiving primary prophylaxis. Secondly, a sufficient period before and after the treatment should be set, and the utility value measured in the real-world. In addition, Based on the results of this study, the cost-effectiveness of pegfilgrastim should be discussed in many countries with universal health care system similar to Japan.

4. Experimental

4.1. Calculation of cost-effectiveness

Using various parameters, we calculated the expected cost and quality-adjusted life year (QALY) of both groups. Next, we calculated the incremental cost-effectiveness ratio (ICER) and performed a cost-utility analysis.
The threshold in the cost-utility analysis was set at 50,000 USD/QALY based on patients' willingness to pay 5,000,000 JPY in Japan (Dulisse et al. 2013), which is 50,000 USD in the United Status (Morrison et al. 2001).

4.2. ICER calculation

ICER (Cost/QALY) = (expected cost of pegfilgrastim group - expected cost of no pegfilgrastim group) ÷ (acquisition QALY of pegfilgrastim group - acquisition QALY of no pegfilgrastim group).

4.3. Analysis position

We valued it from the position of a public health payer.

4.4. Sensitivity analysis

The sensitivity analysis was performed because various parameters of the decision tree analysis model in this study may change. To include uncertainty in the simulated cost-effectiveness analysis, we conducted deterministic and probabilistic uncertainty analyses using a tornado diagram. We selected the parameters, such as the drug cost, FN utility, FN treatment cost, and FN incidence rate.

4.5. Analysis software

TreeAge Pro Healthcare 2020 (Tree Age software Inc., Williamstown, MA) was used as the analysis software for the decision tree analysis model.

4.6. Research ethics and patient consent

This study does not deal directly with patient personal information and was not subject to ethical review as it involves simulations based on previous studies.

Conflicts of interest: The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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