Journal of Clinical Trials
ISSN: 2167-0870

Toriyama et al., J Clin Trials 2018, 8:4
DOI: 10.4172/2167-0870.1000355

Protocol Open Access

Study Protocol for Prospective Observational Study 1 on the Prognosis of Patients with Unresectable Advanced Gastrointestinal and Pancreatic Neuroendocrine Tumors (PROP-UP 1 Study) in Japan

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Received date: September 19, 2018; **Accepted date:** October 20, 2018; **Published date:** October 24, 2018

Abstract

Objective: Although neuroendocrine neoplasm (NEN) is considered to be rare, the incidence rate of gastroenteropancreatic NENs (GEP-NENs) has increased recently, based on the United States' Surveillance, Epidemiology, and End Results (SEER) and epidemiological data from Japan. However, for the internal organs, incidence rates of pancreatic NENs (PanNENs) and hindgut-derived NENs were higher in Japan, while that of midgut-derived NENs was lower, suggesting differences in patient backgrounds between Japan and overseas. Because of differences in patient backgrounds between Japan and overseas, no previous observational studies on the prognosis of advanced GEP-NENs exist in Japan. Therefore, the present study aimed to clarify the actual status of advanced GEP-NENs in Japan by surveying the prognosis of NEN patients diagnosed with curative unresectable disease or recurrent disease following curative resection.

Methods: This was a multicenter observational study of a historical cohort that would investigate the prognosis of GEP-NEN patients diagnosed with unresectable disease or having recurrent disease after curative resection based on imaging results (PROP-UP 1). At enrolment, demographics values, baseline values and survival event information are electronic case report form via a web-based, and after enrollment, the patient is observed prospectively. The primary endpoint of this study was overall survival starting from the day of diagnosis as curatively unresectable or recurrence after curative resection, while the secondary endpoint was progression-free survival starting from the day of diagnosis as curatively unresectable or recurrence after curative resection.

Discussion: The PROP-UP 1 study is the first observational study to clarify the actual status of advanced GEP-NENs in Japan. The results of this study will provide beneficial information on the improvement of the therapeutic strategy for GEP-NENs.

Keywords: Observational study; Gastroenteropancreatic neuroendocrine neoplasm; Japan

Introduction

Neuroendocrine neoplasm (NEN) is a generic term for tumors derived from neuroendocrine cells that occur in organs throughout the body. Although NEN has been regarded as rare, the incidence rate has increased 6.4-fold in recent years, from an incidence rate of 1.09/100,000 in 1973 to 6.98/100,000 in 2012, based on the United States' Surveillance, Epidemiology, and End Results (SEER) [1]. In particular, the incidence rate of gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) was reported to be 3.56/100,000 [1]. Epidemiological data for 2005 and 2010 have also shown increasing trends for Japan, with the incidence rate of pancreatic neuroendocrine neoplasm (PanNEN) increasing from 1.01/100,000 in 2005 to 1.27/100,000 in 2010, while that of gastrointestinal neuroendocrine neoplasms (GI-NEN) increased from 2.10/100,000 in 2005 to 3.51/100,000 in 2010 [2,3]. Increased awareness of the disease concept and improved diagnostic techniques are considered to be factors underlying these increases [4-6].

However, in terms of the internal organs, SEER reports have described incidence rates for PanNEN, midgut-derived NEN, and hindgut-derived NEN of 0.32/100,000, 0.98/100,000 and 1.06/100,000 in the United States [7], while the incidences in Japan were 1.27/100,000, 0.15/100,000 and 2.12/100,000 respectively [3]. Thus, incidence rates of PanNEN and hindgut-derived NEN were higher in Japan while those of midgut-derived NEN were lower, suggesting differences in patient backgrounds between Japan and overseas [3,7]. To identify differences between patients in Japan and overseas, the patient's background and the results of subgroup analysis regarding progression-free survival (PFS) in the RADIANT 3 trial targeting unresectable, advanced pancreatic neuroendocrine tumor (NET) (which showed a hazard ratio of 0.29 (0.14–0.56) in Asians) were reported to be useful [8]. Moreover, even in a phase III randomized trial of sunitinib to target unresectable, advanced PanNET, subgroup analysis of PFS showed a hazard ratio of 0.35 (0.18–0.70) for non-whites, including Asians [9]. These results indicate that both drugs showed a high response rate in Asians. Even in Japan, the effects of everolimus in the RADIANT 3 trial were shown to differ because the median PFS in the Japanese patient group was 19.45 months and the risk-reduction rate for tumor growth was 81% compared with a median a PFS of 11.0 months overall and a 65% risk-reduction rate for tumor growth [10]. Additionally, the response rate was 9.3% in a phase III randomized trial of sunitinib and the median PFS was 11.4 months, whereas a similar patient group in a Japanese Phase II study showed a response rate of 50.0% and a PFS rate of 71% at 12 months [9,11]. These studies suggested a difference in response rates between Japanese and other populations.

Additionally, the World Health Organization (WHO) 2010 classification, based on the Ki-67 index (%), classified the degree of malignancy as Grade 1 (G1), Grade 2 (G2), and neuroendocrine carcinoma (NEC), and the prognosis worsens as the proliferative capacity of G1, G2, and NEC increases [12-14]. However, others have reported that, as a cut off value for G1 and G2, 5% correlates better with prognosis than 3%, which is stated in the WHO 2010 classification [15,16]. Thus, some researchers have suggested that the cut off value for Ki-67 index (%) in the current grading method should be re-examined, and the current grading method may not be optimal for Japanese populations.

Thus, the present study aimed to clarify the actual status of advanced GEP-NEN in Japan by surveying the prognosis of NEN patients diagnosed with curative unresectable disease or recurrent disease following curative resection. This study was designed with the aim of providing a cornerstone for further improvements in the prognosis of patients with advanced NEN. Because this is the first survey in Japan that evaluates the life prognosis of patients with advanced NEN, it is unclear whether the findings will resemble results presented to date from overseas investigations. We, therefore, decided that we would collect data on life prognosis for this study to plot survival curves for each Grade and examine whether WHO classifications reflect the actual status of life prognosis for NEN in Japan. If they do not, we plan to set new cut off values for the Ki-67 index. Therefore, through this historical cohort study (PROP-UP 1), we will estimate cut off values for G1/G2 classifications based on the Ki-67 index. Additionally, molecular biological differences between well-differentiated neuroendocrine tumors (WDNETs) and poorly differentiated neuroendocrine carcinomas (PDNECs) have been revealed, suggesting that these diseases may have different origins. Differences in the incidences of abnormal *RB1*, *TP53*, *BCL2*, and *DAXX/ATRX* gene expression between WDNETs and PDNECs have also been reported, supporting the hypothesis of different origins for these types of cancer [17]. NEC, as defined by the WHO 2010 classification, includes diseases that have the same disease concept as a disease group that is similar to WDNETs (NET-G3), which have high cell-proliferative capacities, and to PDNECs (NEC-G3) [18]. These diseases show molecular biological differences, such as differences in the frequency of *RB* expression and the presence or absence of KRAS mutation [19]. NET-G3 has also been shown to have a difficult pathology, because it does not respond to platinum, nor does PDNEC [20]. Thus, in this PROP-UP study, we analyzed the NEC category in the WHO 2010 classification by dividing it into histologically well-differentiated and poorly differentiated disease groups.

Methods and Analysis

Study design

The PROP-UP 1 study is designed to survey NEN patients diagnosed with curatively unresectable disease or recurrent disease following curative resection, with the objective of elucidating the actual status of advanced NEN in Japan.

At enrolment, demographics values, baseline values and survival event information are electronic case report form (e-CRF) *via* a web-based, and after enrolment the patient is observed prospectively. Thus, this study is a multicenter observational study of a historical cohort that will investigate the prognosis of GEP-NEN patients diagnosed with unresectable disease or having recurrent disease after curative resection based on imaging results.

The study data center which performs data management and statistical analyses for the observed clinical data of registered patients is the Translational Research Center for Medical Innovation (TRI) Data Center. The study data center provided e-CRF *via* a web-based.

Ethics and registration

This study will be performed in accordance with the Declaration of Helsinki and the ethics guidelines of the Ministry of Health, Labour and Welfare for medical research on human subjects. Each facility participating in this study will conduct this research after obtaining approval from its ethics review board. This study has been registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000015976).

Enrolment

From January 2012 until the date that ethics approval was obtained at each facility, enrolment was conducted for patients with GEP-NEN diagnosed with curatively unresectable disease or recurrent disease after curative resection. All patients met the study entry criteria described below.

Eligibility criteria for inclusion: Inclusion criteria for this study were as follows: 1) Histological diagnosis of NET G1/G2, NEC or mixed adenoendocrine carcinoma (MANEC); 2) Diagnosis of curatively unresectable or recurrent disease after curative resection from January 2012 until the date that ethics approval was obtained at each facility; 3) Primary tumor site was either the pancreas or the gastrointestinal tract; 4) Age ≤ 80 years at the time informed consent was obtained; 5) Informed consent to participate in the study obtained from the patient or from a representative, such as an individual with parental authority over the patient or a person who was able to speak on behalf of the patient's intention and in the interest of the patient, in cases where the patient was ≤ 20 years old.

Eligibility criteria for exclusion: Exclusion criteria for this study were as follows: 1) Patients treated for NEN within 1 year before diagnosis of curatively unrespectable disease or with recurrence after curative resection (however, patients will be excluded if they undergo curative resection, or receive pre- or postoperative adjuvant therapy); 2) Patients with double-cancers (synchronous); 3) In recurrent cases after curative resection, patients who could undergo radical resection; 4) Patients who had already been registered to the study at another medical institution; and 5) The physician-in-charge determined that participation in this study was inappropriate for any other reason.

Study period and schedule

The patient enrolment period was 2 years, from January 1, 2014 through December 31, 2015. The observation end-date will be December 31, 2018 (3 years from the end of case registration). It is assumed that the observation period for this study will be extended to December 31, 2021.

At enrolment, patient' data included demographics values, baseline values and survival event information are recorded in e-CRF. Following enrolment, prospectively, annual data will be collected once each year, on December 31, until the observation end-date (Table 1).

Item	At diagnosis of unresectable/ recurrent disease	At enrolment	At time of scheduled reporting					
			2016	2017	2018	2019	2020	2021
Patient background characteristics	○							
Anamnesis/complications	○							
Disease information	○							
Histopathological diagnosis	○							
Overall condition	○	○	○	○	○	○	○	○
Information at onset (only for patients with recurrence after curative resection)	○							
Treatment information for NEN		○	○	○	○	○	○	○
Outcome			○	○	○	○	○	○
Exacerbation of NEN		○	○	○	○	○	○	○

*It is assumed that the observation period of this study will be extended to December 31, 2021. NEN, neuroendocrine neoplasm○To be performed, checked, or observed

Table 1: Schedule for observation, testing and reporting

Endpoints

The primary endpoint of this study is overall survival (OS) starting from the day of diagnosis as curatively unresectable or recurrence after curative resection, while the secondary endpoint is the PFS starting from the day of diagnosis as curatively unrespectable or recurrence after curative resection. As an important stratification item, the Ki-67 index (%) will be stratified according to the WHO classification (G1, ≤ 2%; G2, 3 to 20%; NEC, >20%). Stratification will then be performed using 2%, 5%, 10%, or any other arbitrary value as cut off values for

G1/G2, and analysis will be performed to determine the cut off value that is most appropriate for predicting prognosis of NET patients.

Sample size

A 2010 epidemiological survey reported 355 patients treated annually for unrespectable PanNET and 265 patients treated annually for GI-NET, for a total of 620 new patients during the year [21]. Because this study uses retrospective enrolment during 2 years, about 1/12th of the number of patients treated per year are estimated to be enrolled. Thus for this study, the target number of enrolled patients was set at 100. When the 5-year survival rate for NET patients is estimated 27%, the 100 patient's cohort can be observed 57-89 death case with over 95% probability. This is the number of patient cases for which it is possible to analyze factors related to event occurrence.

Statistical analysis

Based on the WHO 2010 classification, enrolled patients will be divided into three groups, and for OS and PFS the cumulative survival curve using the Kaplan–Meier method, event incidence rate (per person year), and the 95% confidence interval based on a Poisson distribution are estimated. We will also perform analysis using G1/G2 cut off value combinations ≤ 5% for G1 and 6-20% for G2, and ≤ 10% for G1 and 11-20% for G2.

We will apply the proportional hazard model including the Ki-67 index, demographic variables and baseline variables as covariates to examine factors affecting survival. Summary statistics for the Ki-67 index classification stratified by these covariates will also be calculated, and uniformity will be examined by analysis of variance. On non-NEC patients with a Ki-67 index <20%, time-dependent receiver operating characteristic (ROC) curves with censored survival time data will be created by gradually increasing the cut off for G1/G2 from lowest to highest value. ROC curves will be created with both using an unadjusted hazard ratio and an adjusted hazard ratio, which includes as covariates the factors that are considered to be strongly related to prognosis and that are independent of the Ki-67 index (%). Based on these results, we will estimate the G1/G2 cut off for the Ki-67 index. Next, using these estimated G1/G2 cut off values, patients will be divided into three groups (G1, G2, or NEC) and the cumulative survival curves using the Kaplan–Meier method, event incidence rate, and 95% confidence intervals will be estimated.

Additionally, patients will be stratified by primary site (i.e., pancreas or digestive tract) and divided into three groups (G1, G2, or NEC) based on the estimated G1/G2 cut off value above method. Cumulative survival curves using the Kaplan–Meier method, event incidence rate, and 95% confidence intervals will then be estimated. Similar stratified analyses will be also performed for cut off value based on the WHO 2010 classification.

Discussion

The ongoing PROP–UP Study consists of the PROP–UP 1 Study and the prospective PROP–UP 2 Study. The PROP–UP 1 Study is a historical cohort study investigating the life prognosis of patients with NEN in the gastroenteropancreatic area and who are diagnosed as curatively unresectable or as having recurrence after curative resection. Differences such as patient background and effects of pharmacotherapy have been clarified for NEN patients between Japan and the West. However, in Japan, no observational studies have reported on the life prognosis and similar results for advanced NEN patients, and the actual life prognosis status with this disease is not well understood. The present study aims to elucidate that status and also to investigate whether the grading system proposed by the WHO is appropriate for Japanese populations. Additionally, we intend to clarify the optimal Ki-67-based grades to use with Japanese patients. In the 2017 WHO classification, the NEC category from the WHO 2010 classification has been reclassified histologically into well-differentiated tumors and poorly differentiated tumors. The well-differentiated type has been revised to NET G3, while the poorly differentiated type has been changed to NEC G3. In the PROP–UP 1 Study, the NEC category in the WHO 2010 classification will be histologically classified as well-differentiated tumors (NET G3) and poorly differentiated tumors (NEC G3), and then examined. This will be the first report of a prognostic survey conducted that is consistent with NET G3 and NEC G3, as defined in the WHO 2017 classification, and the findings should be useful. Finally, to verify the results of PROP-UP 1, we have planned the PROP-UP 2 study, which is multicenter observational study that will investigate the prognosis of a GEP-NEN patients diagnosed as unresectable or with recurrent disease after curative resection based on imaging results (Figure 1).

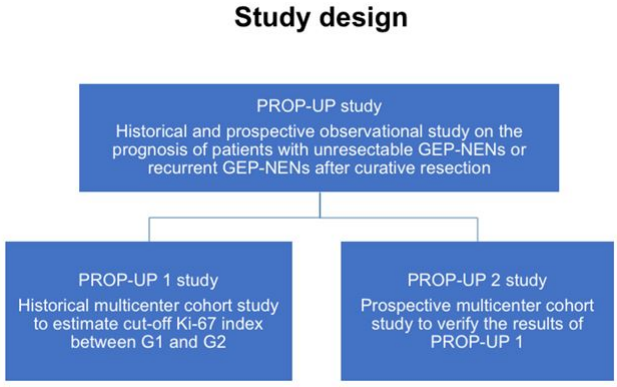

Figure 1: Study concept for the PROP-UP study. GEP-NENs, gastroenteropancreatic neuroendocrine neoplasms; G1, grade 1; G2, grade 2

Competing Interests

T.O. has received honoraria from Bristol-Myers Squibb, Nippon chemifa, EA Pharma, FUJIFILM RI Pharma, Astellas Pharma, Nippon Kayaku, Celgene, MSD, and Teijin Pharma; research grants from Kowa, Takeda Bio Development Center, OncoTherapy Science, Kyowa Hakko Kirin, Shizuoka Industry and Glaxo Smith Kline; honoraria and research grants from Novartis Pharma, Pfizer Japan, Bayer Yakuhin, Chugai Pharmaceutical, Yakuruto Honsha, Eisai, AstraZeneca, Merck Serono, Baxter, and Nobelpharma; research grants and advisory fees from Nippon Boehringer Ingelheim, Nano Carrier, and Zeria Pharmaceutical; an advisory fee and an honorarium from Daiichi Sankyo; and advisory fees, honoraria, and research grants from Dainippon Sumitomo Pharma, Eli Lilly, and Ono Pharmaceutical. M.T. has received honoraria from Ono Pharmaceutical, Yakult Honsha, MSD, Taiho Pharmaceutical, Daiichi Sankyo, Merck, Chugai Pharmaceutical, and Kyowa Hakko Kirin. H.Y. has received an honorarium from Pfizer Japan. S.N. has received an honorarium from Eisai. H.I. has received honoraria from Yakult Honsha, Eli Lilly Japan,

Nobelpharma, Mochida Pharmaceutical, Astellas Pharma, Chugai Pharmaceutical, and Eisai; research funding from Taiho Pharmaceutical; and had an advisory role for Ono Pharmaceutical. S.I. has received honoraria from Taiho Pharmaceutical, Chugai Pharmaceutical, MSD, Takeda Pharmaceutical, and Asahi Kasei Pharmaceutical. N.M. has received honoraria from Novartis, Zeria Pharmaceutical, NanoCarrier, Eisai, MSD, Dainippon Sumitomo Pharma, Yakult Honsha, Pfizer Japan, Kyowa Hakko Kirin, Taiho Pharmaceutical, Merck Serono, AstraZeneca, and Teijin Pharma, Ono Pharmaceutical, Incyte Inc, ASLAN Pharmaceuticals, Pharma Valley Center, Elli Lilly Japan K.K. All other authors have no conflicts of interest.

Funding

This study was supported by Novartis Pharma K.K.

Author's contributions

TI was the chief investigator. TI and MI conceptualized and designed the study and drafted the protocol manuscript. All authors participated in the study and contributed to obtaining the data for this study. YT contributed to management of the data. MS and TK are contributed as study data center and TK is trial statistician. KT and SH drafted this manuscript. All authors contributed to revising the manuscript, and all approved the final manuscript.

Acknowledgments

We would like to express our sincere gratitude to the 29 physicians who participated in case registration for this study, as well as to the staff at Novartis Pharma Co., Ltd. and the TRI Data Center who supported this research.

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