Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Prevention of Neutropenia with Pegfilgrastim on Day 3 of TPF Chemotherapy in Advanced Head and Neck Squamous Cell Carcinoma: A Prospective Phase II Study (PROCEED trial)

Yuki Saito

saitou.tky@gmail.com

the University of Tokyo

Kenya Kobayashi

the University of Tokyo

Osamu Fukuoka

the University of Tokyo

Koji Yamamura

the University of Tokyo

Rumi Ueha

the University of Tokyo

Chisato Fujimoto

the University of Tokyo

Mikio Ogura

the University of Tokyo Hospital

Mariko Inoue

the University of Tokyo Hospital

Kenji Kondo

the University of Tokyo

Article

Keywords: Head and neck cancer, Febrile neutropenia, Granulocyte colony-stimulating factor, Pegfilgrastim, TPF chemotherapy, Docetaxel

Posted Date: June 3rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9550229/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Purpose

TPF chemotherapy (docetaxel, cisplatin, and 5-fluorouracil) is the standard induction regimen for advanced head and neck squamous cell carcinoma (HNSCC) but carries a high risk (10%–20%) of febrile neutropenia (FN). Although prophylactic granulocyte colony-stimulating factor (G-CSF) therapy is recommended, the optimal timing of pegfilgrastim remains largely unknown. This phase II trial aimed to evaluate the safety and efficacy of pegfilgrastim administered on day 3 of TPF chemotherapy.

Methods

This single-arm phase II study enrolled patients with stage III–IVB HNSCC receiving TPF induction or definitive chemotherapy. The regimen included docetaxel (60 or 50 mg/m² with concurrent radiotherapy), cisplatin (60 mg/m²), and 5-fluorouracil (600 mg/m²/day) for 5 days. Pegfilgrastim (3.6 mg) was administered subcutaneously on day 3. The primary endpoint was the incidence of first-cycle FN. Secondary endpoints included fever, neutropenia, and tumor response.

Results

Between July 2023 and August 2025, 18 patients were recruited (median age 55.5 years; 18 males), none of whom developed FN (0%, 95% CI: 0–18.5%). Fever without neutropenia occurred in 5 patients (31%), whereas neutropenia (absolute neutrophil cell count < 1000/mm³) developed in 1 patient. The tumor control rate on day 21 was 87.5% (14/16 evaluable patients). Adverse events occurred in 8 patients (44.4%), including two serious cases (fever requiring antibiotics), all of which resolved. No treatment discontinuation was required.

Conclusion

Pegfilgrastim administered on day 3 of TPF chemotherapy had an acceptable safety profile, enabling the safe delivery of TPF therapy without FN in advanced HNSCC.

Trial registration

Japan Registry of Clinical Trials (jRCTs031220695), First posted 07/03/2023. Available at https//jrct.mhlw.go.jp/enlatestdetail/jRCTs031220695

Introduction

Head and neck cancers account for approximately 2.8% of all cancer diagnoses in Japan, with approximately 29,000 new cases and 8,600 deaths reported annually [1]. For locally advanced head and neck squamous cell carcinoma (HNSCC) based on the TNM classification, standard treatment options include concurrent chemoradiotherapy or surgery followed by adjuvant therapy [2].

Induction chemotherapy has been developed to improve laryngeal preservation and treatment outcomes, particularly for advanced laryngopharyngeal cancers [3]. The TPF regimen (docetaxel, cisplatin, and 5-fluorouracil) has become the standard induction chemotherapy regimen, demonstrating superior efficacy compared to PF (cisplatin and 5-fluorouracil) regimens [4]. However, TPF therapy has been associated with significant hematologic toxicity, with febrile neutropenia (FN) having been reported in 9%–12% of patients and treatment-related mortality in approximately 3% [4, 5].

Prophylactic granulocyte colony-stimulating factor (G-CSF) is recommended for chemotherapy regimens associated with a febrile neutropenia (FN) risk of 10–20% [6]. Pegfilgrastim, a pegylated form of filgrastim with sustained G-CSF activity, offers the advantage of a single-dose administration per chemotherapy cycle. According to the package insert, pegfilgrastim should be administered at least 24 hours after completion of chemotherapy to avoid potential enhancement of chemotherapy-induced myelosuppression. However, the optimal timing of pegfilgrastim administration during TPF therapy remains uncertain. In TPF regimens that include a 5-day continuous infusion of 5-fluorouracil, strict adherence to the 24-hour rule would delay pegfilgrastim administration until day 6 or later. This timing may be suboptimal because docetaxel, administered on day 1, is the principal myelosuppressive agent in TPF, and the neutrophil nadir typically occurs 7–10 days after its administration. Linot et al. reported that pegfilgrastim administration on day 3 of TPF therapy effectively prevented FN without additional safety concerns. Moreover, the cytotoxic effects of 5-fluorouracil are relatively mild compared with those of docetaxel, which may reduce the risk of excessive neutropenia when G-CSF stimulation is administered during ongoing 5-fluorouracil infusion.

Unfortunately, prospective clinical trials supporting this approach in head and neck cancer patients are currently lacking. Therefore, this phase II trial was conducted to evaluate the safety of pegfilgrastim administered on day 3 of TPF chemotherapy for advanced HNSCC.

Methods

Study design and oversight

This single-center, single-arm, open-label phase II trial was conducted at The University of Tokyo Hospital (Tokyo, Japan). This study was approved by the University of Tokyo Clinical Research Review Board (approval number: 2022508SP), was registered with the Japan Registry of Clinical Trials (jRCTs031220695; First posted: 7/03/2023; available at: https://jrct.mhlw.go.jp/en-latest-detail/jRCTs031220695), and conducted in accordance with the Clinical Trials Act of Japan, the Declaration of Helsinki, and Good Clinical Practice guidelines. All patients provided written informed consent before enrollment.

Patients

Eligible patients were the adults aged 18–80 years with histologically confirmed stage III, IVA, or IVB HNSCC who were scheduled to receive TPF either as induction therapy or definitive concurrent chemoradiotherapy. Additional inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate organ functioning defined as an absolute neutrophil count ≥ 1,500/mm³, hemoglobin levels ≥ 9.0 g/dL, platelet count ≥ 100,000/mm³, total bilirubin levels ≤ 2.0 mg/dL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤ 100 U/L, and estimated creatinine clearance (Cockcroft–Gault formula) or estimated glomerular filtration rate ≥ 60 mL/min.

Exclusion criteria were as follows: fever ≥ 38.0°C upon enrollment; white blood cell count ≤ 2,000/mm³; severe hepatic, renal, or cardiovascular conditions (grade ≥ 3 based on JCOG-CTCAE version 5.0); active secondary malignancies (including leukemia); severe bone marrow suppression or active infection; history of severe drug allergies; hypersensitivity to pegfilgrastim or other G-CSF products; concurrent or recent (within 7 days) use of tegafur–gimeracil–oteracil potassium; psychiatric disorders interfering with the patient's capacity to provided informed consent; pregnancy or lactation; and any condition deemed unsuitable by the investigators.

Treatment

Patients enrolled in this trial were all diagnosed with HNSCC and scheduled for the initial curative treatment. Eligibility for TPF therapy was determined based on the need for a waiting period of 6 weeks or longer prior to radical resection for hypopharyngeal or nasal/paranasal sinus cancers or the desire to increase CDDP-RT treatment intensity for unresectable oropharyngeal cancer.

TPF chemotherapy consisted of docetaxel (60 mg/m² for induction therapy or 50 mg/m² for concurrent chemoradiotherapy) administered via intravenous infusion for 1 h on day 1, cisplatin (60 mg/m²) on day 1, and 5-fluorouracil (600 mg/m²/day) administered via continuous intravenous infusion for 5 days (days 1–5). Each cycle comprised 21 days. For patients receiving concurrent chemoradiotherapy, irradiation doses were delivered at 2 Gy per fraction, once daily, 5 days per week for 21 days.

Pegfilgrastim (3.6 mg) was injected subcutaneously on day 3 of each TPF cycle. Standard supportive care, including antiemetics (palonosetron, dexamethasone, and aprepitant) and hydration was provided according to institutional guidelines. Prophylaxis with antibiotics was prohibited.

Assessments

During hospitalization, patients were monitored daily through clinical assessments, vital signs, and body temperature measurements. Laboratory evaluations, including complete blood count and comprehensive metabolic panel, were performed on days 0, 4, 8, 10, 15, and 21 and upon the occurrence of fever. Contrast-enhanced computed tomography or magnetic resonance imaging was performed at baseline and on day 21.

FN was defined as an absolute neutrophil count < 500/mm³ (or < 1,000/mm³ with an expected decline to < 500/mm³ within 48 h) with an axillary temperature of ≥ 37.5°C (or oral temperature ≥ 38.0°C) according to the Febrile Neutropenia Clinical Practice Guidelines (2nd edition). Fever was defined as an axillary temperature ≥ 37.5°C. Neutropenia was defined as an absolute neutrophil count < 1,000/mm³. Adverse events were graded according to JCOG-CTCAE version 5.0.

Tumor response was assessed through imaging on day 21 using the following criteria: complete response (CR), complete visual disappearance of all targeted tumors; partial response (PR), ≥ 30% decrease in the sum of target lesion diameters; progressive disease (PD), ≥ 20% increase or clear progression; and non-CR/non-PD, outcomes not meeting the criteria for CR, PR, or PD. Tumor control rate was defined as the proportion of patients achieving CR, PR, or non-CR/non-PD.

Endpoints

The primary endpoint was the incidence of FN during the first cycle of TPF chemotherapy (through day 21). Secondary endpoints included the incidence of fever (regardless of neutrophil count), incidence of neutropenia, tumor control rate at day 21, and incidence and severity of adverse events.

Statistical analysis

This exploratory phase II trial was designed to evaluate the efficacy of day 3 pegfilgrastim administration in preventing FN. Based on published data showing TPF-associated FN rates of 10%–15%, we considered an FN rate of ≤ 5% to be clinically beneficial. With a true FN rate of 5%, the probability of observing ≥ 3 FN cases in 18 patients was < 6%. Therefore, we set the target sample size to 18 patients. If ≥ 3 FN cases occurred (≥ 15%), pegfilgrastim would be considered ineffective for FN prevention, whereas if ≤ 2 FN cases occurred, further evaluation would be warranted.

Sequential interim analysis was performed after completing the observation period. If 3 FN cases occurred, the trial would be terminated for futility. The primary analysis was performed on the per-protocol set (PPS), defined as patients who completed one TPF cycle and received pegfilgrastim. The full analysis set (FAS) was defined as all enrolled patients who received at least one dose of study medication without major protocol violations. Safety analysis was conducted in all patients who received at least one dose of the study medication.

For the primary endpoint, we calculated the point estimate and exact 95% confidence interval (CI) using the Clopper–Pearson method. For continuous variables, the descriptive statistics (n, mean, standard deviation, minimum, median, maximum) and 95% CI for mean values based on t-distribution were reported. Categorical variables were reported as frequencies and proportions with 95% CI. No multiplicity adjustment was conducted for secondary endpoints.

Results

Patient characteristics and treatment

Between July 2023 and August 2025, 18 patients were enrolled and received treatment. All 18 patients comprised the safety analysis set and FAS. Two patients underwent surgery on day 20 before completing the full 21-day cycle and were excluded from the PPS, which comprised 16 patients. The median age was 55.5 years (range: 22–79), with all 18 patients (100%) being male. The primary tumor sites included the oropharynx (n = 5, 28%), nasal cavity/ethmoid sinus (n = 4, 22%), hypopharynx (n = 3, 17%), nasopharynx (n = 2, 11%), maxillary sinus (n = 2, 11%), and others (n = 2, 11%). Disease stage distribution was stage III (n = 9, 50%), IV (n = 1, 6%) IVA (n = 4, 22%), and IVB (n = 4, 22%). ECOG performance status was 0 in 16 patients (89%) and 1 in 2 patients (11%). Moreover, 17 patients (94%) received TPF as induction chemotherapy, whereas 1 patient (6%) received TPF with concurrent chemoradiotherapy. The baseline characteristics of the included patients are summarized in Table 1.

Table 1
Baseline patient characteristics

Characteristic	N = 18
Age, years	
Median (range)	55.5 (22–79)
Sex, n (%)	
Male	18 (100)
Female	0 (0)
Primary site, n (%)	
Oropharynx	5 (28)
Nasal cavity/ethmoid sinus	4 (22)
Hypopharynx	3 (17)
Nasopharynx	2 (11)
Maxillary sinus	2 (11)
Other	2 (11)
Disease stage, n (%)	
III	9 (33)
IV	1 (6)
IVA	4 (22)
IVB	4 (22)
ECOG PS, n (%)	
0	16 (89)
1	2 (11)
Treatment regimen, n (%)	
TPF induction	17 (94)
TPF + concurrent RT	1 (6)

Primary endpoint: Febrile neutropenia

No cases of FN were observed in either the FAS (0/18, 0%; 95% CI: 0%–18.5%) or PPS (0/16, 0%; 95% CI: 0%–20.6%) during the first TPF cycle through day 21. Hence, the trial did not meet the predefined futility criterion (≥ 3 FN cases), indicating a potential clinical benefit of day 3 pegfilgrastim administration.

Secondary endpoints

In the PPS, fever (≥ 37.5°C) occurred in 5 of the 16 patients (31%; 95% CI: 11.0–58.7%). All five patients with fever had an absolute neutrophil count > 1,000/mm³ upon fever onset. Two patients developed infections (pneumonia and bacteremia) that were classified as serious adverse events but resolved with antibiotic therapy and supportive care (Fig. 1).

One patient in the PPS developed neutropenia (absolute white blood cell count 700/mm³) at day 8 (1/16, 6.3%; 95% CI: 0–30.3%) (Fig. 2). Among the 16 evaluable patients in the PPS, tumor response on day 21 showed that no patient had CR (0%), 14 had PR (87.5%), and 2 had PD (12.5%), yielding a tumor control rate of 87.5% (95% CI: 61.7%–98.4%) .

Safety

All 18 patients underwent pegfilgrastim therapy on day 3, as scheduled. Adverse events occurred in 8 patients (44.4%; 95% CI: 21.5–69.2%). Fever was the most commonly detected adverse event (5 patients, 27.8%), followed by diarrhea (3 patients, 16.7%). Two patients (11.1%) experienced serious adverse events: one patient presented with pneumonia and another with bacteremia, both accompanied by fever. Both conditions were managed with appropriate antimicrobial therapy and supportive care, enabling to achieve complete resolution. No study discontinuations were required due to adverse events. No pegfilgrastim-related adverse events, such as bone pain or splenomegaly, were observed. Detailed adverse event data are reflected in Table 2.

Table 2
Adverse events

Adverse Event	Any Grade, n (%)	Grade ≥ 3, n (%)
Any adverse event	8 (44.4)	2 (11.1)
Fever	5 (27.8)	2 (11.1)
Diarrhea	3 (16.7)	0
Facial erythema	1 (5.6)	0
Anemia	1 (5.6)	1 (5.6)
Abdominal pain	1 (5.6)	0

Discussion

This prospective phase II trial demonstrated that prophylactic pegfilgrastim administered on day 3 of TPF chemotherapy can effectively prevent febrile neutropenia (FN) in patients with advanced HNSCC. None of the 18 enrolled patients developed FN during the first TPF cycle which was substantially lower than historically reported FN rates of 10%–20% with TPF therapy [4,5]. Additionally, only one patient

exhibited neutropenia (absolute neutrophil count 700/mm³), suggesting that the regimen was well-tolerated with no treatment discontinuations required due to adverse events.

Linot et al. first reported the safety and efficacy of day 3 pegfilgrastim administration in patients with head and neck cancer undergoing DCF chemotherapy, where the reduced FN incidence without additional safety concerns was demonstrated [7]. Our study confirms and extends these findings in the prospective phase II trial with rigorous monitoring and predefined endpoints. The rationale for day 3 administration is that 5-fluorouracil has relatively mild cytotoxic effects compared to docetaxel, thus minimizing the theoretical risk of excessive neutropenia in concomitant G-CSF and 5-fluorouracil infusion. A similar strategy had been employed for esophageal cancer, with a retrospective study by Yoshimoto et al. reporting that early PEG-G administration on days 3–5 decreased the incidence of FN [8].

Although FN was completely prevented, 31% of the patients experienced fever without neutropenia. Five patients had fever episodes, two of which were associated with documented infections (pneumonia and bacteremia), classified as serious adverse events. However, both cases resolved with appropriate antimicrobial therapy. This finding suggests that while pegfilgrastim effectively prevents neutropenia, fever may still occur due to infections or other causes. Clinicians should therefore maintain vigilance for infectious complications even in the absence of this condition.

The observed tumor control rate of 87.5% on day 21 in our study is consistent with the expected TPF response rates, suggesting that pegfilgrastim administration on day 3 does not compromise antitumor efficacy. This is an important finding considering concerns about the potential interference of G-CSF with chemotherapy efficacy. The high response rate observed in our study, combined with the absence of FN, supports the use of this regimen to enable the safer delivery of full-dose TPF therapy.

FN prevention has important clinical implications beyond patient safety. FN often necessitates chemotherapy dose reductions or treatment delays, thereby potentially deteriorating treatment outcomes [9]. In the context of induction chemotherapy, maintaining dose intensity is crucial for achieving optimal tumor response and enabling subsequent definitive therapy. For patients receiving concurrent chemoradiotherapy, treatment interruptions can negatively impact locoregional control. By preventing FN, day 3 pegfilgrastim administration can elevate treatment completion rates and ultimately enhance clinical outcomes.

Our study has several limitations. First, this was a single-arm trial without a control group, which limited our ability to make direct comparisons with alternative G-CSF strategies or no prophylactic measures. However, given the well-established FN rate of 10%–20% achieved with TPF therapy, the complete absence of FN in our study provides strong evidence of its clinical benefit. Second, the sample size was relatively small (n = 18), reflecting the exploratory phase II design. Third, our study only evaluated the first TPF cycle. Hence, data on subsequent cycles would be valuable but were beyond the scope of this trial, which focused on the FN prevention during initial therapy. Fourth, the TPF dose used was reduced to 80% of the doses validated in clinical trials. This reduced dose is intended for nasopharyngeal carcinoma

patients scheduled for subsequent chemoradiation [10]. Although considered appropriate for subjects similar to those included in the current cohort, who were scheduled to undergo surgery or CCRT later, the efficacy of this dosage regimen remains unknown. Finally, this trial was a single-center study conducted at a specialized academic institution, which potentially limited the generalizability of our results.

In conclusion, prophylactic pegfilgrastim administered on day 3 of TPF chemotherapy can effectively prevent febrile neutropenia in patients with advanced HNSCC, with an acceptable safety profile. This therapeutic regimen allows for a safer delivery of full-dose TPF therapy and can increase treatment completion rates. These findings support the incorporation of day 3 pegfilgrastim into standard prophylactic strategies for patients undergoing TPF chemotherapy for HNSCC. Further studies are warranted to evaluate this approach in larger patient cohorts and across consecutive TPF cycles.

Statements & Declarations

Acknowledgments

The authors would like to thank Enago (www.enago.com) for critically reviewing the manuscript draft.

Funding statement: This work was supported by institutional funding from the University of Tokyo

Competing Interests: The authors have no relevant financial or non-financial interests to disclose.

Author Contributions:

Yuki Saito: Conceptualization, Formal analysis, Funding acquisition, Visualization, Methodology, Writing-original draft, Writing-review and editing of the article. Kenya Kobayashi: Validation,Methodology, Writing-review and editing of the manuscript. Osamu Fukuoka: review and revision of the article, development of the methodology, analysis of the data, and review and revision of the article. Koji Yamamura: Review and revision of the manuscript. Rumi Ueha: Review and revision of the manuscript. Chisato Fujimoto: Review and revision of the manuscript. Fumiharu Nakajima: Clinical Research Support Services. Mariko Inoue: Clinical Research Support Services. Mikio Ogura: Clinical Research Support Services. Kenji Kondo: Resources,Supervision, Validation, Project administration,and Writing-review and editing of the article.

Ethics approval: This study was approved by the University of Tokyo Clinical Research Review Board (approval number: 2022508SP)

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Data availability statement: The datasets generated and analyzed during the current study are not publicly available due to patient privacy and ethical restrictions but are available from the corresponding author on reasonable request and with permission of the institutional review board.

References

1. Cancer Statistics. Cancer information service, national cancer center, Japan (National Cancer Registry, Ministry of Health, Labour and Welfare). Jan (2026). https://ganjoho.jp/reg_stat/statistics/data/dl/index.html. Accessed 12.
2. National Comprehensive Cancer Network. Head and neck cancer version 1. (2026). https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed 12 Jan 2026.
3. Department of Veterans Affairs Laryngeal Cancer Study Group et al. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl. J. Med.* **324**, 1685–1690. https://doi.org/10.1056/NEJM199106133242402 (1991).
4. Posner, M. R. et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl. J. Med.* **357**, 1705–1715. https://doi.org/10.1056/nejmoa070956 (2007).
5. Vermorken, J. B. et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl. J. Med.* **357**, 1695–1704. https://doi.org/10.1056/nejmoa071028 (2007).
6. Smith, T. J. et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. *J. Clin. Oncol.* **33**, 3199–3212. https://doi.org/10.1200/JCO.2015.62.3488 (2015).
7. Linot, B. et al. Efficacy and safety of early G-CSF administration in patients with head and neck cancer treated by docetaxel-cisplatin and 5-fluorouracil (DCF protocol): a retrospective study. *Support Care Cancer*. **22**, 2831–2837. https://doi.org/10.1007/s00520-014-2270-8 (2014).
8. Yoshimoto, T. et al. Pegfilgrastim for the management of neutropenia during neoadjuvant chemotherapy with docetaxel, cisplatin, and 5-fluorouracil in esophageal cancer patients. *Int. J. Clin. Oncol.* **29**, 142–148. https://doi.org/10.1007/s10147-023-02438-3 (2024).
9. Lyman, G. H. et al. The impact of the granulocyte colony-stimulating factor on chemotherapy dose intensity and cancer survival: a systematic review and meta-analysis of randomized controlled trials. *Ann. Oncol.* **24**, 2475–2484. https://doi.org/10.1093/annonc/mdt226 (2013).
10. Sun, Y. et al. Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. *Lancet Oncol.* **17**, 1509–1520. https://doi.org/10.1016/S1470-2045(16)30410-7 (2016).

Figures

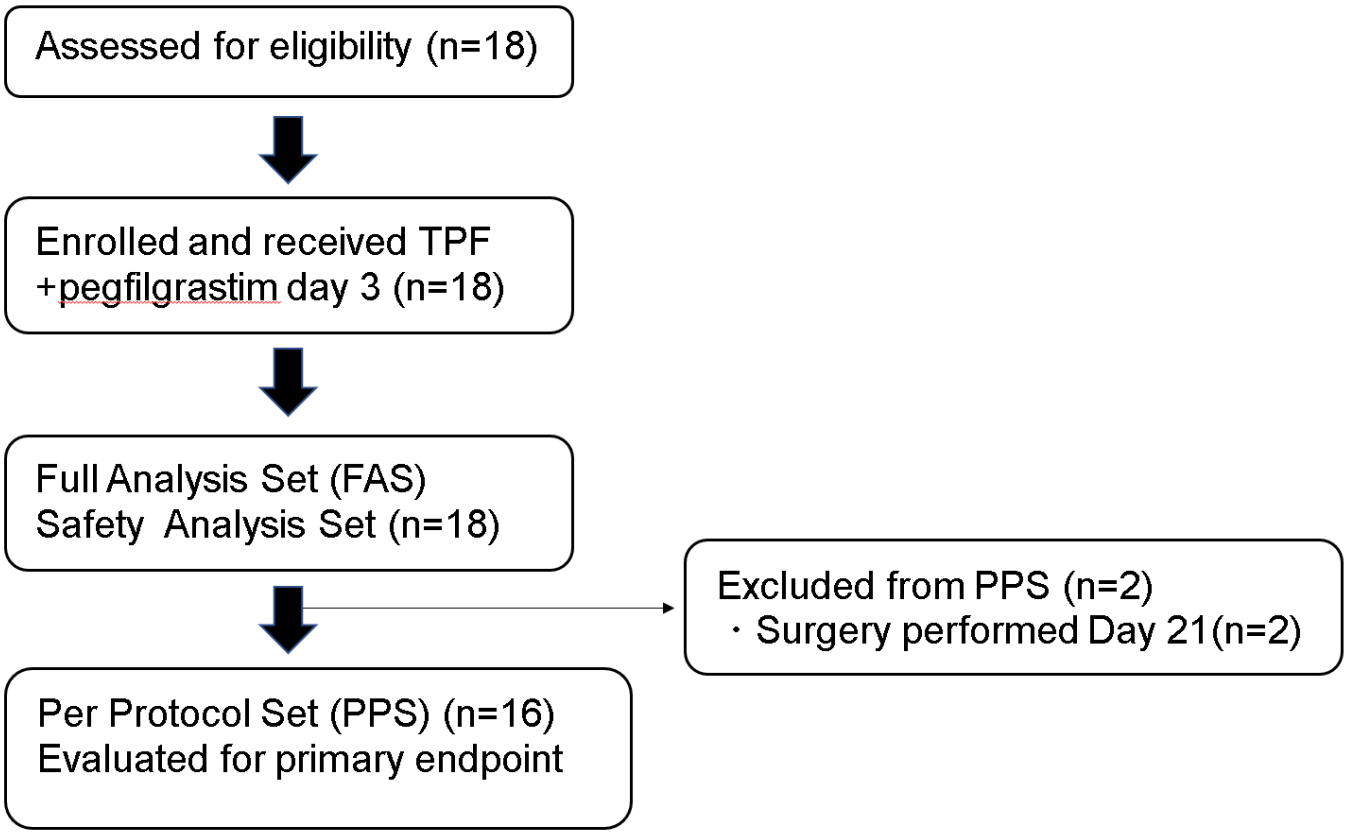


Figure 1

Figure 1

CONSORT Flow Diagram

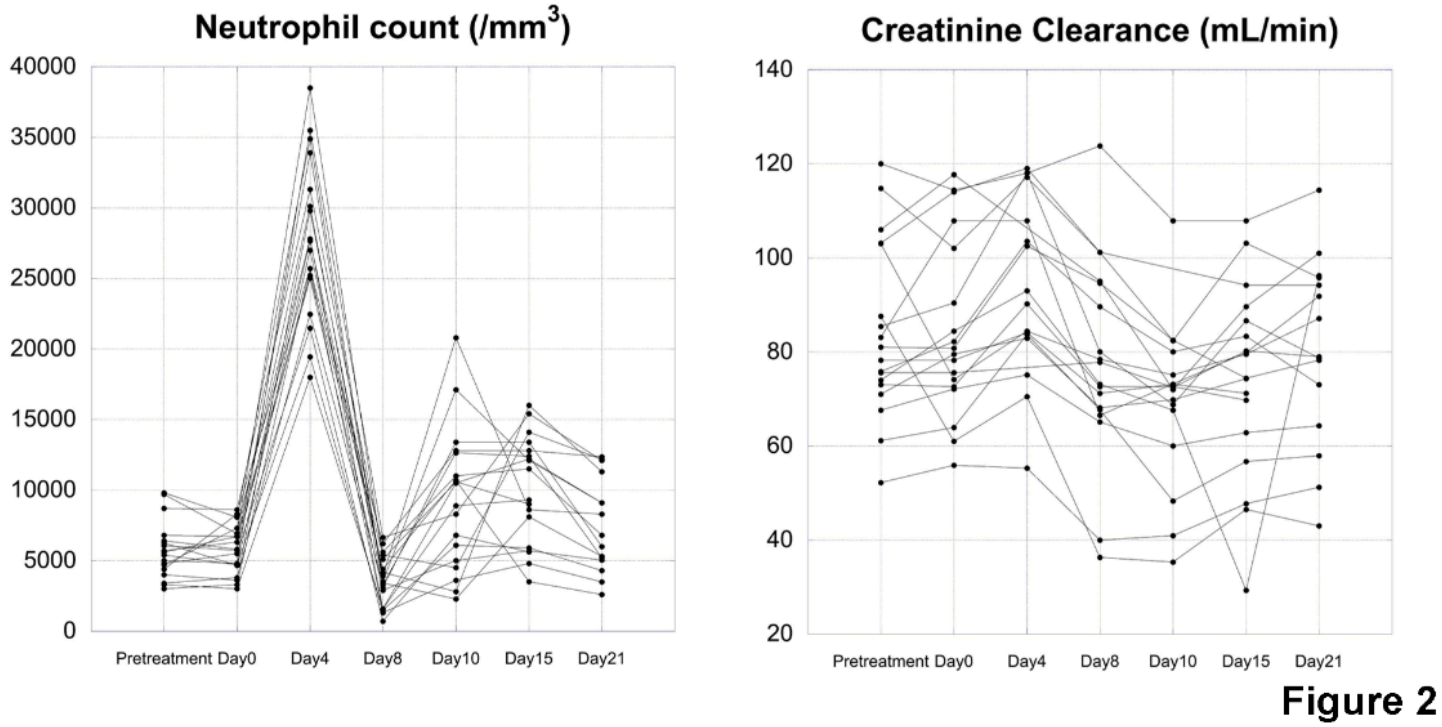


Figure 2

The time course of peripheral blood neutrophil cell counts and creatinine clearance during the examination period for cases enrolled in the main trial. The most significant decrease in neutrophil cell counts occurred on day 8; only one case exhibited a decrease below 1000 (minimum value, 700). Furthermore, no cases showed a decrease in creatinine clearance on day 21 compared to pre-treatment levels that would significantly impact post-treatment outcomes