Prophylactic use of pegfilgrastim enables the management of severe neutropenia without dose delays in patients with metastatic colorectal cancer treated with TAS-102 plus bevacizumab

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Received July 11, 2021; Accepted March 1, 2022

DOI: 10.3892/mco.2022.2536

Abstract. Combined treatment with bevacizumab and trifluridine/tipiracil (TAS-102) leads to an increased chance of survival in patients with refractory metastatic colorectal cancer (mCRC); however, this treatment is associated with an increased frequency of severe neutropenia (number of neutrophils <1,000), which should ideally be managed without dose delays. The present study provided a retrospective review of 35 patients with mCRC, and aimed to elucidate the benefits of prophylactic pegfilgrastim for the treatment of severe neutropenia. Patients received TAS-102 (35 mg/m^2) orally twice daily on days 1-5 and 8-12 of each 28-day treatment cycle, along with intravenous bevacizumab (5 mg/kg) on days 1 and 15. Moreover, the patients received 3.6 mg pegfilgrastim on day 15 of each cycle. The incidence of adverse events (AEs), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS) were assessed. In the first and subsequent cycles, 23 and 12 patients, respectively, received pegfilgrastim. The most common AE experienced was grade 3/4 neutropenia (8 patients; 22.9%). Among these 8 patients, 6 (17.1%) and 3 (8.6%) exhibited neutropenia prior to receiving pegfilgrastim or following discontinuation of pegfilgrastim administration, respectively. Moreover, 1 individual among these 8 patients (2.9%) demonstrated grade 3 neutropenia both prior to receiving pegfilgrastim and following discontinuation of pegfilgrastim. A total of 2 patients (5.7%) exhibited grade 3 bone pain, which prevented sustainable administration of pegfilgrastim and resulted in grade 3 neutropenia. Dose delays and dose reduction of TAS-102 due to neutropenia were required in 5 (14.3%) and 2 (5.7%) patients, respectively, during the treatment period. None of the patients exhibited severe neutropenia during chemotherapy after pegfilgrastim administration, thereby preventing dose delays and dose reduction of TAS-102. The relative dose intensity was 96.8% (65.0-100.0%), and the DCR was 54.3%. The median PFS and median OS were 4.4 and 14.9 months, respectively. In conclusion, prophylactic pegfilgrastim may facilitate the management of severe neutropenia without dose delays in patients with mCRC treated with TAS-102 plus bevacizumab.

Introduction

Trifluridine/tipiracil (TAS-102) is an oral anticancer agent that comprises trifluridine and tipiracil hydrochloride. Trifluridine exhibits anticancer activity through its ability to incorporate into the DNA by substitution for thymidine (1), whereas tipiracil hydrochloride works as a thymidine phosphorylase inhibitor and prevents the degradation of trifluridine, which maintains the blood concentration of trifluridine (1,2). A global randomized controlled trial of TAS-102 (RECOUSE trial; https://clinicaltrials.gov/ct2/show/NCT01607957) for patients with refractory metastatic colorectal cancer (mCRC) demonstrated that TAS-102 significantly prolonged overall survival (OS) and progression-free survival (PFS) compared with a placebo-based treatment (3). In a phase II trial (C-TASK FORCE; https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000015039) the combined treatment of TAS-102 with bevacizumab demonstrated survival benefits for patients with mCRC in a refractory setting. However, combined treatment of bevacizumab with TAS-102 increased the frequency of neutropenia of grade 3 or higher up to 77% and that of febrile neutropenia (FN) up to 16%, necessitating

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Abbreviations: AE, adverse events; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; TAS-102, trifluridine/tipiracil; mCRC, metastatic colorectal cancer; G-CSF, granulocyte colony-stimulating factors; FN, febrile neutropenia; ECOG, Eastern Cooperative Oncology Group; CR, complete response; PR, partial response; PD, progressive disease; NSAIDs, non-steroidal anti-inflammatory drugs

Key words: pegfilgrastim, filgrastim, neutropenia, TAS-102, bevacizumab

treatment interruption (3). Thus, adequate management of neutropenia is critical to ensure the effectiveness of combined TAS-102 and bevacizumab treatment in prolonging the survival in salvage lines.

Recombinant human granulocyte colony-stimulating factors (G-CSFs), including pegfilgrastim and filgrastim, are widely used to manage severe neutropenia. G-CSFs reduce the incidence of infection in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy (4-6). The National Comprehensive Cancer Network guidelines (7) (NCCN Clinical Practice Guidelines in Oncology; NCCN Guidelines®; Myeloid Growth Factors Version 2. 2017) recommend prophylactic use of G-CSFs in patients with cancer, based on the chemotherapy regimen and patient-related risk factors, particularly for the high- (>20%) and intermediate-risk (10-20%) groups (8). In the C-TASK FORCE trial, 16% of patients were reported to develop FN, which indicated that the combined treatment of TAS-102 with bevacizumab harbors an intermediate risk of FN (9). Pegfilgrastim is a long-acting pegylated form of G-CSF with a sustained duration of action, and a single dose is comparable to daily injections of filgrastim (5 g/kg/day) for 10-11 days (10). Furthermore, pegfilgrastim reduced the incidence of FN in patients with advanced colorectal cancer who received FOLFOX (or FOLFIRI) plus bevacizumab (11).

The present study aimed to further elucidate the benefits of the prophylactic use of pegfilgrastim for severe neutropenia, and verified the efficacy and safety of the combined treatment of TAS-102 with bevacizumab.

Materials and methods

Patients. A total of 35 patients with mCRC, including 16 males and 19 females, were recruited for the present retrospective analysis. The median age of the patients was 69 years (range, 29-80 years) and their Eastern Cooperative Oncology Group (ECOG) performance status (PS) was used for an indicator of general condition. Patients with a PS of 0, 1 or 2 were recruited for the present retrospective analysis. Numerous previous treatments, including oxaliplatin, irinotecan, and 5-Fluorouracil were acceptable. The patients were treated with TAS-102 plus bevacizumab between April 2016 and December 2020 at Saitama Medical Center, Jichi Medical University (Saitama, Japan). Patients did not receive TAS-102 plus bevacizumab if they exhibited uncontrollable hypertension, a history of thrombosis or embolism within the 6 months, or a history of gastrointestinal perforation or severe hemorrhage.

The present study was approved by the Research Ethics Committee of Jichi Medical University (approval no. R19-30; Saitama, Japan) and conducted in accordance with the principles of The Declaration of Helsinki. Written informed consent was obtained from all participants before administering chemotherapy, in accordance with the guidelines of the Jichi Medical University Institutional Review Board.

Treatment schedule. The patients received treatment according to a 28-day regimen of the C-TASK FORCE, in which 35 mg/m^2 of TAS-102 was administered orally twice daily on days 1-5 and 8-12 in the 28-day cycle. Moreover, 5 mg/kg of bevacizumab was administered by intravenous infusion for 30 min every 2 weeks, on days 1 and 15. The patients also received a single subcutaneous pegfilgrastim injection of 3.6 mg on day 15 of every 28-day cycle. The median number of treatment cycles were 11 (range, 2-32 cycles). Treatment was continued until the disease progressed, levels of unacceptable toxicity were reached, ECOG PS deteriorated to >2 or patient consent was withdrawn.

Efficacy and safety assessment. The incidence of adverse events (AEs), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS) were assessed. DCR was defined as the percentage of patients who have achieved complete response (CR), partial response (PR) and a stable disease status following therapeutic intervention. PFS was defined as the length of time from the start of TAS-102 plus bevacizumab treatment to either disease progression or death. OS was defined as the interval from the start of TAS-102 plus bevacizumab treatment to death from any cause. Tumors were evaluated every 2 or 3 months using computed tomography (CT) scanning or positron emission tomography/CT imaging for initial tumor staging. Tumor response and progression were evaluated according to the Response Evaluation Criteria in Solid Tumors (version 1.1) (12). AEs were graded according to the Common Terminology Criteria for Adverse Events (version 4.0) (13). Treatment was continued until the disease progressed, levels of unacceptable toxicity were reached, ECOG PS deteriorated to >2 or patient consent was withdrawn. The median follow-up period was 13.1 months (range, 2.1-35.2 months).

Statistical analysis. Statistical analyses were performed using StatView 5.0.1 (SAS Institute Inc.). The OS and PFS curves were analyzed using the Kaplan-Meier method, and intergroup differences were compared using the log-rank test. Data are presented as the median and range. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics and treatment. The characteristics of the 35 patients, including 16 males and 19 females, are displayed in Table I. The median age of the patients was 69 years (range, 29-80 years). ECOG PS 0 was observed in 16 patients, PS 1 was observed in 15 patients and PS 2 in 4 patients. All patients were treated with at least one regimen before receiving TAS-102 plus bevacizumab. All patients started at the full dose of TAS-102 and received 3.6 mg pegfilgrastim for primary prophylaxis. The median follow-up period was 13.1 months (range, 2.1-35.2 months). No dose modification was performed using bevacizumab. A total of 23 patients received pegfilgrastim at day 15 of the first 28-day cycle, 8 patients received it in the second cycle, 3 in the third cycle and 1 in the fifth cycle. The treatment time course within 12 months in 35 patients is displayed in Fig. 1, and includes the number of leucocytes and neutrocytes before and during the treatment with TAS-102 plus bevacizumab. The time course and use of pegfilgrastim is displayed in Fig. 2.

Table I. Characteristics of patients.

Characteristic	Value
Median age (range), years	69 (29-80)
Sex, n	
Male	16
Female	19
ECOG PS, n	
0	16
1	15
2	4
Primary site of tumor, n	
Right-sided colon	7
Left-sided colorectum	28
Primary lesion resection, n	
Yes	28
No	7
Metastatic organs, n	
1	18
2	16
≥3	1
KRAS mutation, n	
No, wild-type	25
Yes, mutant	10
Number of previous therapies, n	
1	4
2	15
3	8
4	3
5	5
Prior systemic anticancer agents, n	
Fluoropyrimidine	35
Irinotecan	33
Oxaliplatin	34
Bevacizumab	31
Anti-EGFR monoclonal antibody	15
Regorafenib	2

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; PS, performance status; *KRAS*, GTPase *KRAS*.

Safety and AEs. AEs are summarized in Table II. The most common AEs (experienced in ≥30% patients) of any grade were leukopenia, neutropenia, anemia, fatigue, hypertension, anorexia, nausea and diarrhea. The most frequent AEs of grade 3 or worse were leukopenia (n=5, 14.3%), neutropenia (n=8, 22.9%), anemia (n=5, 14.3%) and bleeding (n=1, 2.9%). FN was seen in 1 patient (2.9%), but it occurred before the patient received pegfilgrastim. A total of 2 patients (5.7%) with grade 3 neutropenia required an antiemetic drug. No treatment-related deaths occurred.

Neutropenia at grade 3 or worse was identified in 8 patients (22.9%) prior to receiving pegfilgrastim or following discontinuation of pegfilgrastim administration. A total of 6 patients (17.1%) exhibited symptoms before receiving pegfilgrastim (case 2, 8, 9, 15, 18 and 33; 'before' in occurrence of neutropenia of Fig. 1). Each case is indicated by a red asterisk (*) of time course in Figs. 1 and 2. A total of 3 patients (8.6%) displayed symptoms after discontinuing pegfilgrastim. Case 1 and 19 exhibited grade 3 neutropenia following the discontinuation of treatment, due to worsened PS and progression in disease, respectively. Case 18 demonstrated grade 3 neutropenia both prior to receiving pegfilgrastim and after discontinuation of pegfilgrastim. Moreover, case 23 displayed grade 3 leukopenia after discontinuation of treatment due to bleeding. Each case is delineated by a red double asterisk (**) of time course in Figs. 1 and 2. Patients who received pegfilgrastim for primary prophylaxis did not exhibit severe neutropenia.

Dose delays due to neutropenia during the treatment period were required in 5 patients [14.3%; neutropenia in dose delay (neutropenia) in Fig. 1]. These neutropenia-induced drug delays appeared in patients before they received pegfilgrastim or after discontinuation of pegfilgrastim administration. The time course of 5 patients who required dose delays before taking pegfilgrastim are shown in cases 2, 8, 9, 15 and 33. Each case is shown as 'D' in red of time course in Figs. 1 and 2. Among these patients, cases 2 and 15 required dose delays due to the discontinuation of pegfilgrastim. Dose delays due to non-hematological AEs during the treatment period were required in 3 patients [8.6%; dose delay (others) in Figs. 1 and 2]. A total of 2 patients (5.7%) demonstrated grade 3 bone pain (cases 8 and 15), which resulted in the discontinuation of pegfilgrastim (Figs. 1 and 2). Grade 3 bone pain prevented sustainable administration of pegfilgrastim in case 15. The time course with the treatment of pegfilgrastim is displayed in Fig. 2. Grade 3 neutropenia occurred when the patient was not undergoing pegfilgrastim treatment, which resulted in dose delays and administration of filgrastim ('F' in time course in case 15 of Fig. 2). A total of 1 patient displayed grade 3 fatigue, resulting in a dose delay (case 9). Patients who received regular administration of pegfilgrastim for primary prophylaxis did not exhibit dose delays. Although sustainable administration of pegfilgrastim was not sufficiently achieved in the years after the introduction of pegfilgrastim, improvements have been observed since the middle of 2018 (Fig. 2).

A total of 8 patients (22.8%) required a dose reduction due to adverse events; namely, anemia (3 patients), neutropenia (2 patients), fatigue (2 patients) and diarrhea (1 patient; reasons for dose reduction in Fig. 1). Although 2 patients required a dose reduction of TAS-102 due to neutropenia while they were not taking pegfilgrastim, no further dose reduction was required after taking pegfilgrastim (cases 2 and 15 in Fig. 2). A total of 2 patients required a dose reduction due to anemia, as shown in cases 8 and 11 ('anemia' in reasons for dose reduction in Figs. 1 and 2). The relative dose intensity was 96.8% (65.0-100.0%). A total of 24 patients (77.2%) received 1-3 more subsequential chemotherapy regimens, whereas 8 patients (22.8.%) were treated with the best supportive care to improve quality of life without chemotherapy.

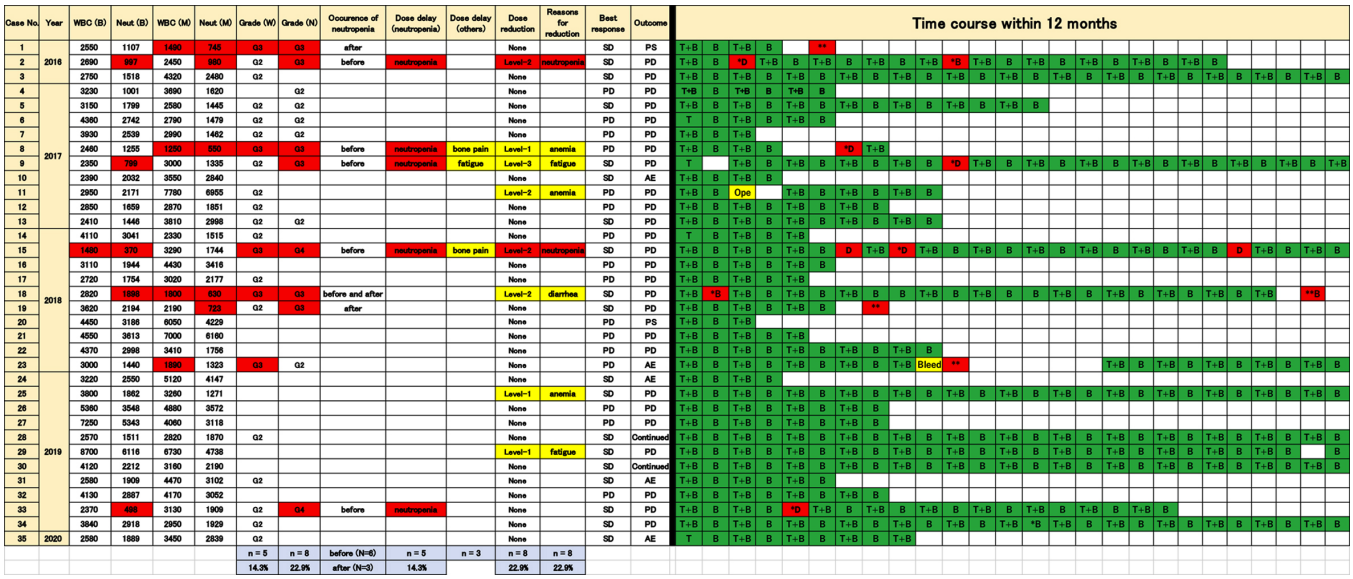

Figure 1. Time course of the treatments within 12 months in connection with safety, adverse events and efficacy in 35 patients treated with TAS-102 plus bevacizumab. Safety, adverse events and efficacy in 35 patients are shown on the left side of the figure, and the time course of the treatments within 12 months is shown on the right. The Y-axis indicates patients ordered by year of chemotherapy. The X-axis in the time course indicates the treatment procedure during chemotherapy. WBC (B), the number of leucocytes before the treatment of pegfilgrastim; Neut (B), the number of neutrocytes before the treatment of pegfilgrastim; WBC (M), minimum number of leucocytes before the treatment of pegfilgrastim; Neut (M), minimum number of neutropenia before the treatment of pegfilgrastim; Grade (W), grade of leukopenia; Grade (N), grade of neutropenia; Continued; chemotherapy is continued; T + B, TAS-102 + bevacizumab; B, bevacizumab; *In red, grade 3 or worse neutropenia [corresponding numbers of leucocytes and neutrocytes are shown in the WBC (B), WBC (B), WBC (M) and Neut (M) in red when these adverse events occurred]; **In red, grade 3 or worse neutropenia occurred after discontinuation of treatments with TAS-102 plus bevacizumab; B in red, treatment with bevacizumab without dose delay. Ope, operation; Bleed, bleeding; SD, stable disease; PD, progressive disease; PS, performance status; AE, adverse event; D, dose delay; TAS-102, trifluridine/tipiracil; WBC, white blood cell; Neut, neutrocyte.

Efficacy. No patients exhibited CR or PR; however, 19 patients (54.3%) exhibited a stable disease state. The DCR was 54.3%. A total of 16 patients (45.7%) exhibited progressive disease (PD). The median PFS period was 4.4 months (3.3-7.1 months; Fig. 3A). The median OS was 14.9 months (9.9-24.0 months; Fig. 3B). The association between metastatic sites and PFS revealed no significant difference in patients with liver (n=21), lung (n=9) or peritoneum metastasis (n=12; 4.2, 3.3 and 4.4 months, respectively; Fig. 3A). With regards to OS, patients with peritoneum metastasis exhibited poor outcomes, but there was no significant difference between OS and patients with liver, lung or peritoneum metastasis (20.4, 24.6 and 9.8 months, respectively; Fig. 3B). In addition, a significant difference was not identified between PFS (4.4 and 3.5 months) or OS (7.3 and 6.1 months) and patients with single or multiple metastases, respectively (Fig. 3C and D).

Regarding the kirsten rat sarcoma virus oncogene homolog (*KRAS*) status and its association with treatment outcomes, the median PFS was 4.1 months (1.4-24.9 months) in 25 patients with wild-type *KRAS* and 5.6 months (2.8-36.1 months) in 10 patients with mutant RAS (Fig. 3E). In 25 patients with wild-type *KRAS*, the median OS was 10.0 months (2.1-35.4 months) and in patients with mutant *KRAS*, the median OS was 23.7 months (12.3-36.1 months; Fig. 3F). There was no significant difference between PFS or OS and patients with or without *KRAS* mutations.

Discussion

The present study demonstrated the benefits of pegfilgrastim in patients receiving TAS-102 plus bevacizumab for the management of neutropenia. Prophylactic use of pegfilgrastim prevented dose delays or dose reductions of TAS-102, resulting in improved survival time in the salvage line. To the best of our knowledge, the present retrospective analysis is the first to demonstrate the potential prophylactic use of pegfilgrastim for appropriate management of neutropenia in patients receiving TAS-102 plus bevacizumab.

Neutropenia is a major AE associated with chemotherapy in patients with advanced CRC (14,15). The additional use of bevacizumab in chemotherapy increases the risk of all and high-grade neutropenia (16). Results of previous studies demonstrated that among patients receiving TAS-102, grade 3 or higher neutropenia was reported to be the most frequent AE experienced (3,9). TAS-102 monotherapy induced grade 3 or higher neutropenia in 38% of patients in the RECOUSE trial (3), and TAS-102 plus bevacizumab induced grade 3 or higher neutropenia in 72% of the patients in the C-TASK FORCE trial (9). Fujii *et al* (17) demonstrated that TAS-102 plus bevacizumab treatment was associated with a higher risk of neutropenia when compared with TAS-102 monotherapy, suggesting that TAS-102 plus bevacizumab is required for adequate management of neutropenia. Results of the present study demonstrated that grade 3 or higher neutropenia was most frequently observed in 22.9% of patients, which was lower than the 72% incidence rate in patients receiving TAS-102 plus bevacizumab in the C-TASK FORCE trial, and comparable to the 38% incidence rate in those receiving TAS-102 monotherapy in the RECOUSE trial (3). Moreover, neutropenia was not observed in patients treated with pegfilgrastim. The present study identified 3 patients with grade 3 neutropenia or leucopenia after discontinuing pegfilgrastim, due to worsening

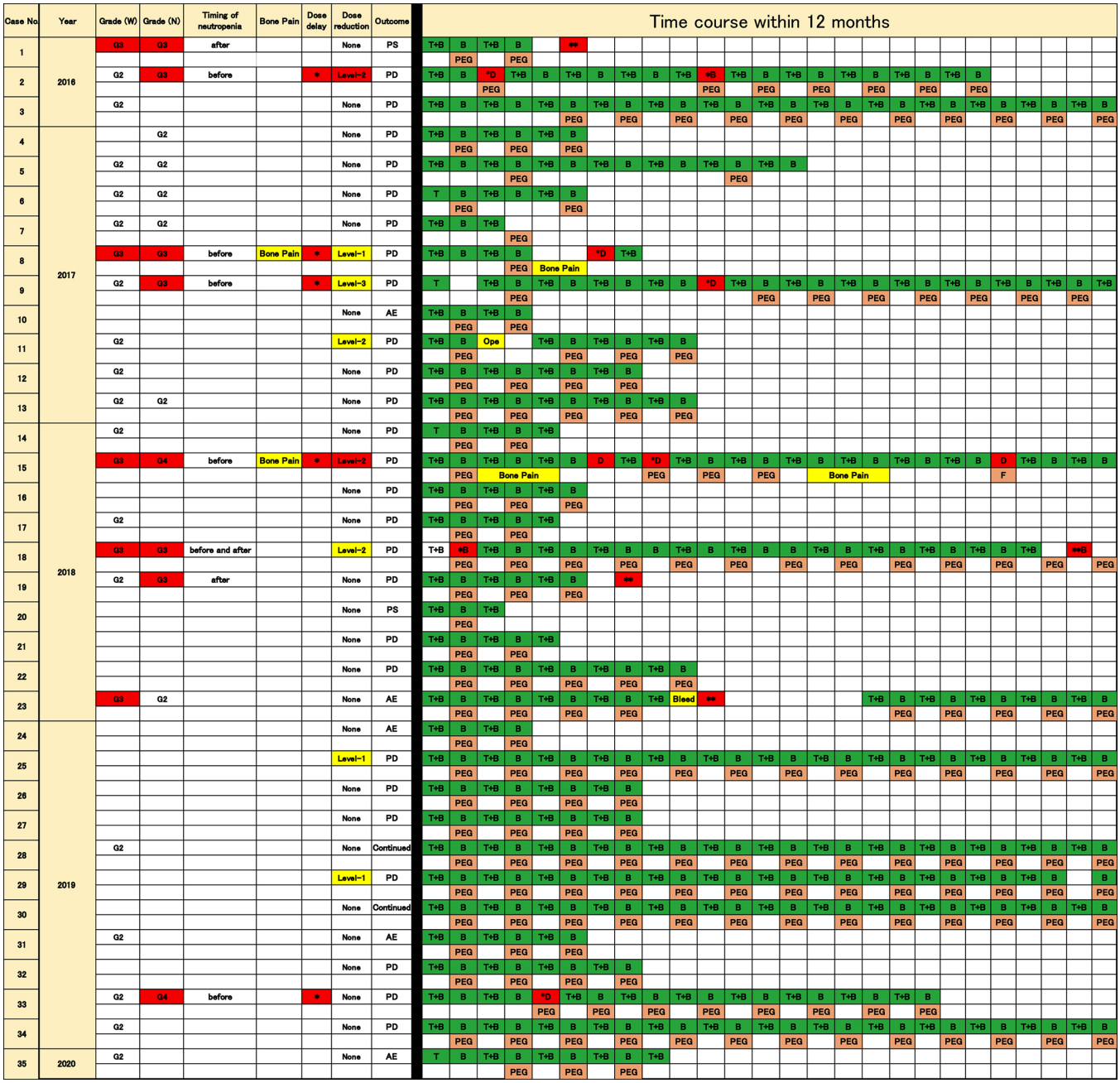

Figure 2. Time course and treatment of pegfilgrastim within 12 months in 35 patients treated with TAS-102 plus bevacizumab. Safety, adverse events and efficacy in 35 patients are shown on the left side of the figure and the time course of the treatments within 12 months is shown on the right. The Y-axis indicates patients ordered by year of chemotherapy. The X-axis in the time course indicates the treatment procedure during chemotherapy. Grade (W), grade of leukopenia; Grade (N), grade of neutropenia; Continued; chemotherapy is continued; T + B, TAS-102 + bevacizumab; B, bevacizumab; *In red, grade 3 or higher neutropenia; **In red, grade 3 or higher neutropenia occurred after discontinuation of treatment with TAS-102 plus bevacizumab; B in red, treatment with bevacizumab without dose delay. Ope, operation; F, filgrastim; Bleed, bleeding; PD, progressive disease; PS, performance status; AE, adverse event; PEG, pegfilgrastim; D, dose delay; TAS-102, trifluridine/tipiracil.

PS, PD and AE; therefore, close management of neutropenia is required following the discontinuation of treatment.

The incidence of FN has been reported to increase with regimens containing bevacizumab (18). The pegfilgrastim and anti-vascular endothelial growth factor Evaluation Study trial (the PAVES trial; https://clinicaltrials.gov/ct2/show/NCT00911170) was conducted to evaluate the effect of pegfilgrastim on the incidence of grade 3/4 FN in patients with locally advanced CRC or mCRC receiving bevacizumab combined with first-line FOLFOX or FOLFIRI (11). Grade 3/4 FN was observed in 2.4% of the patients who received pegfilgrastim and in 5.7% of those who received a placebo. Thus, the incidence of grade 3/4 FN declined by >50% following administration of pegfilgrastim. The odds ratio of 0.41 calculated in the PAVES trial indicated that the risk of FN was reduced to 59%. In comparison, TAS-102 plus bevacizumab increased the risk of FN by up to 16% in the C-TASK FORCE trial. In the present study, 1 patient (2.9%) experienced FN following treatment with TAS-102 plus bevacizumab, which occurred prior to administration of pegfilgrastim.

Table II. Adverse events affecting patients during the study treatment period.

A, Hematological adverse events

Adverse event	Any grade, n (%)	Grade 3/4, n (%)
Leucopenia	26 (74.3)	5 (14.3)
Neutropenia	22 (62.9)	8 (22.9)
Anemia	23 (65.7)	5 (14.3)
Thrombocytopenia	15 (42.9)	0 (0.0)

B, Non-hematological adverse events

Adverse event	Any grade, n (%)	Grade 3/4, n (%)
Fever	4 (11.4)	1 (2.9)
Febrile neutropenia	1 (2.9)	1 (2.9)
Fatigue	31 (88.6)	3 (8.6)
Hypertension	11 (31.4)	0 (0.0)
Anorexia	16 (45.7)	1 (2.9)
Nausea	24 (68.6)	2 (5.7)
Vomiting	7 (20.0)	0 (0.0)
Diarrhea	24 (68.6)	3 (8.6)
Constipation	9 (25.7)	1 (2.9)
Proteinuria	29 (82.9)	1 (2.9)
Bone pain	4 (11.4)	2 (5.7)
Bleeding	0 (0.0)	1 (2.9)

Dose intensity has been reported to be an important factor influencing treatment outcomes. A high relative dose intensity (RDI) with a threshold of 85% has been identified as an independent factor for improving outcomes in different cancers, including breast cancer, lymphoma (19) and CRC (20,21). G-CSF supports the maintenance of a high RDI of myelosuppressive chemotherapy. The patients in the present study exhibited a high RDI of 96.8%, owing to the prophylactic use of pegfilgrastim. A total of 8 patients (22.8%) required at least one dose reduction of TAS-102 in the present study. This was similar to the findings observed in the C-TASK FORCE trial (24%), although the RDI of 96.8% observed in the present study was higher than that in the C-TASK FORCE trial (81.3%). Neutropenia-induced dose delays were observed during the treatment period in 84% of the patients in the C-TASK FORCE trial, whereas 5 patients (14.3%) required dose delays during the treatment period, owing to the prophylactic use of pegfilgrastim in the present study. Furthermore, no dose delays were observed when pegfilgrastim was administered.

An improvement of treatment outcomes was expected in the present study due to the intensification of dose intensity and prevention of dose delays. Results of the present study demonstrated a longer OS (14.9 months) compared with that in the C-TASK FORCE trial (11.4 months), whereas the PFS of 4.4 months was lower than that in the C-TASK FORCE trial (5.7 months). Moreover, the present study included 4 patients with a PS of 2, and these patients exhibited a shorter PFS. The exclusion of these 4 patients resulted in a PFS of 5.3 months (data not shown), suggesting that PS was an important factor that influenced the selection of patients more likely to benefit from TAS-102 plus bevacizumab. However, stable conditions without severe neutropenia and drug interruption may have contributed to the subsequential treatments of TAS-102 plus bevacizumab, which would have resulted in the prolonged OS (14.9 months) in the present study.

Bone pain is a pegfilgrastim-induced clinical problem that may result in discontinuation of pegfilgrastim and lead to less effective chemotherapy dosing (22). Kirshner *et al* (22) reported an overall pain incidence of 59%, with 24% of the patients experiencing severe bone pain. In the present study, two patients (5.7%) experienced grade 3 bone pain, which resulted in the discontinuation of pegfilgrastim, suggesting that interventions for pegfilgrastim-induced bone pain are required. Non-steroidal anti-inflammatory drugs (NSAIDs) have been reported to be effective in preventing or decreasing the incidence and/or severity of this pegfilgrastim-induced bone pain (22); therefore, NSAIDs were administered to those who experienced bone pain. However, after severe bone pain occurs, patients may refuse to continue taking pegfilgrastim; therefore, detailed information should be provided to patients to facilitate management of pegfilgrastim-induced bone pain with NSAIDs. As an alternative to NSAIDs, loratadine (an antihistamine) should be considered to help prevent bone pain in patients receiving chemotherapy and pegfilgrastim. This is due to high levels of tolerability, ease of administration and other potential benefits (23).

The present study demonstrated promising results with the use of pegfilgrastim for adequate management of neutropenia in patients undergoing treatment with TAS-102 plus bevacizumab. The absence of treatment interruptions may preserve the patients' stable condition, facilitating subsequent treatment and improving OS.

Several limitations of the present analysis must be acknowledged. Namely, the study was conducted with a retrospective design at a single center. Moreover, all enrolled patients with mCRC were Japanese, and the sample size was small; thus, patient diversity was lacking. In addition, pegfilgrastim was not administered to all patients during the first 28-day cycle, and 24.3% of patients received pegfilgrastim during the second cycle or later. Considering these limitations, the findings of the present study may require further verification in a large-scale prospective study.

Prophylactic use of pegfilgrastim enabled the management of severe neutropenia without causing dose delays in patients with mCRC treated with TAS-102 plus bevacizumab. The appropriate management of neutropenia contributed to an improved survival time in the salvage line. Although future studies are required to draw definitive conclusions, the present study may provide a novel theoretical basis for the use of further strategies to circumvent severe neutropenia in patients receiving combination treatment of TAS-102 with bevacizumab. Thus, this may act as a potential treatment option to prolong survival in salvage line therapy.

Acknowledgements

Not applicable.

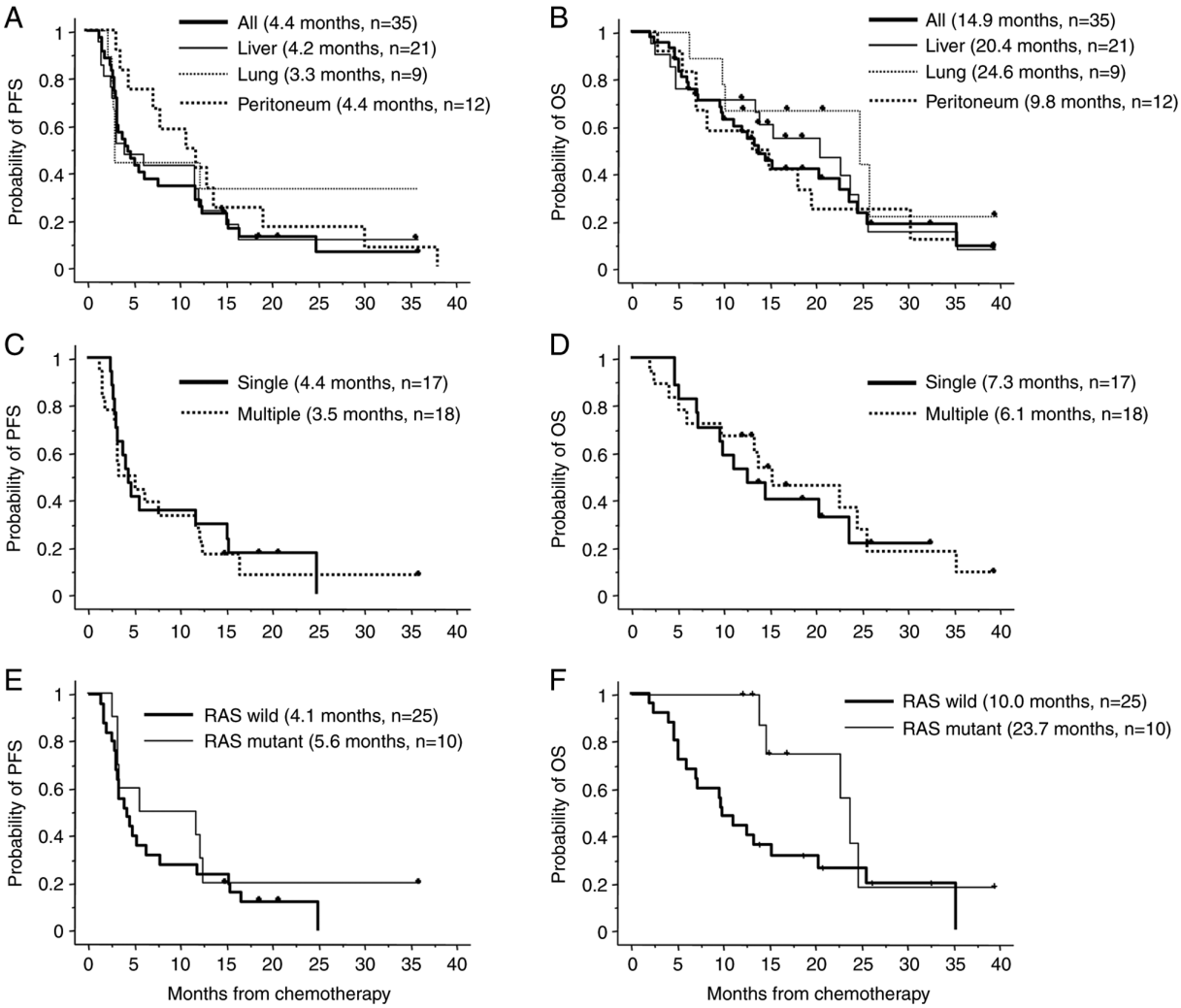

Figure 3. Comparison of PFS and OS in 35 patients according to metastatic sites and *KRAS* status. The X-axis indicates months of chemotherapy; the Y-axis indicates the probability of PFS (left) and OS (18). (A) Comparison of PFS between patients with liver (n=21), lung (n=9) and peritoneal metastasis (n=12), including duplicate patients. (B) Comparison of OS between patients with liver, lung and peritoneal metastasis, including duplicate patients. (C) Comparison of PFS between patients with single (n=17) and multiple metastases (n=18). (D) Comparison of OS between patients with single (n=17) and multiple metastases (n=18). (E) Comparison of PFS between patients with *KRAS* wild (n=25) and *KRAS* mutation (n=10). (F) Comparison of OS between patients with *KRAS* wild (n=25) and *KRAS* mutation (n=10). Median PFS and OS were shown. PFS, progression-free survival; OS, overall survival.

Funding

The present study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology (grant no. JP 16K10514) and the JKA Foundation through its promotion funds from the Keirin Race (grant no. 27-1-068).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. ST and KS confirm the authenticity of all the raw data.

Authors' contributions

All the authors contributed to the study design. ST and KS drafted the manuscript and analyzed the data. ST and HI performed the experiments. All other authors (YK, RM, IA, YE, NK, FW, KF, MS, ST, YM and TR) contributed to sample collection, data collection and interpretation and manuscript review. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Research Ethics Committee of Jichi Medical University (approval no. R19-30; Saitama, Japan) and conducted in accordance with the principles of The Declaration of Helsinki. Written informed consent was obtained from all participants before administering chemotherapy, in accordance with the guidelines of the Jichi Medical University Institutional Review Board.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Tanaka N, Sakamoto K, Okabe H, Fujioka A, Yamamura K, Nakagawa F, Nagase H, Yokogawa T, Oguchi K, Ishida K, *et al*: Repeated oral dosing of TAS-102 confers high trifluridine incorporation into DNA and sustained antitumor activity in mouse models. Oncol Rep 32: 2319-2326, 2014.
2. Fukushima M, Suzuki N, Emura T, Yano S, Kazuno H, Tada Y, Yamada Y and Asao T: Structure and activity of specific inhibitors of thymidine phosphorylase to potentiate the function of antitumor 2'-deoxyribonucleosides. Biochem Pharmacol 59: 1227-1236, 2000.
3. Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, Yamazaki K, Shimada Y, Tabernero J, Komatsu Y, *et al*: Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med 372: 1909-1919, 2015.
4. Crawford J, Dale DC and Lyman GH: Chemotherapy-induced neutropenia: Risks, consequences, and new directions for its management. Cancer 100: 228-237, 2004.
5. Lyman GH, Kuderer N, Greene J and Balducci L: The economics of febrile neutropenia: Implications for the use of colony-stimulating factors. Eur J Cancer 34: 1857-1864, 1998.
6. Lyman GH and Kuderer NM: Filgrastim in patients with neutropenia: Potential effects on quality of life. Drugs 62 (Suppl 1): S65-S78, 2002.
7. Network NCC: National Comprehensive Cancer Network guidelines. 2022.
8. Crawford J, Becker PS, Armitage JO, Blayney DW, Chavez J, Curtin P, Dinner S, Fynan T, Gojo I, Griffiths EA, *et al*: Myeloid growth factors, version 2.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 15: 1520-1541, 2017.
9. Kuboki Y, Nishina T, Shinozaki E, Yamazaki K, Shitara K, Okamoto W, Kajiwara T, Matsumoto T, Tsushima T, Mochizuki N, *et al*: TAS-102 plus bevacizumab for patients with metastatic colorectal cancer refractory to standard therapies (C-TASK FORCE): An investigator-initiated, open-label, single-arm, multicentre, phase 1/2 study. Lancet Oncol 18: 1172-1181, 2017.
10. Morrison VA, Wong M, Hershman D, Campos LT, Ding B and Malin J: Observational study of the prevalence of febrile neutropenia in patients who received filgrastim or pegfilgrastim associated with 3-4 week chemotherapy regimens in community oncology practices. J Manag Care Pharm 13: 337-348, 2007.
11. Pinter T, Klippel Z, Cesas A, Croitoru A, Decaestecker J, Gibbs P, Hotko Y, Jassem J, Kurteva G, Novotny J, *et al*: A phase III, randomized, double-blind, placebo-controlled trial of pegfilgrastim in patients receiving first-line FOLFOX/bevacizumab or FOLFIRI/bevacizumab for locally advanced or metastatic colorectal cancer: Final results of the pegfilgrastim and anti-VEGF evaluation study (PAVES). Clin Colorectal Cancer 16: 103-114, 2017.
12. Schwartz LH, Litière S, de Vries E, Ford R, Gwyther S, Mandrekar S, Shankar L, Bogaerts J, Chen A, Dancey J, *et al*: RECIST 1.1-Update and clarification: From the RECIST committee. Eur J Cancer 62: 132-137, 2016.
13. Institute NC: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. 2010.
14. Falcone A, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, Crinò L, Benedetti G, Evangelista W, Fanchini L, *et al*: Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: The gruppo oncologico nord ovest. J Clin Oncol 25: 1670-1676, 2007.
15. Hecht JR, Pillai M, Gollard R, Heim W, Swan F, Patel R, Dreiling L, Mo M and Malik I: A randomized, placebo-controlled phase ii study evaluating the reduction of neutropenia and febrile neutropenia in patients with colorectal cancer receiving pegfilgrastim with every-2-week chemotherapy. Clin Colorectal Cancer 9: 95-101, 2010.
16. Schutz FA, Jardim DL, Je Y and Choueiri TK: Haematologic toxicities associated with the addition of bevacizumab in cancer patients. Eur J Cancer 47: 1161-1174, 2011.
17. Fujii H, Matsuhashi N, Kitahora M, Takahashi T, Hirose C, Iihara H, Yamada Y, Watanabe D, Ishihara T, Suzuki A and Yoshida K: Bevacizumab in combination with TAS-102 improves clinical outcomes in patients with refractory metastatic colorectal cancer: A retrospective study. Oncologist 25: e469-e476, 2020.
18. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, *et al*: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 350: 2335-2342, 2004.
19. Wildiers H and Reiser M: Relative dose intensity of chemotherapy and its impact on outcomes in patients with early breast cancer or aggressive lymphoma. Crit Rev Oncol Hematol 77: 221-240, 2011.
20. Nakayama G, Tanaka C, Uehara K, Mashita N, Hayashi N, Kobayashi D, Kanda M, Yamada S, Fujii T, Sugimoto H, *et al*: The impact of dose/time modification in irinotecan- and oxaliplatin-based chemotherapies on outcomes in metastatic colorectal cancer. Cancer Chemother Pharmacol 73: 847-855, 2014.
21. Aspinall SL, Good CB, Zhao X, Cunningham FE, Heron BB, Geraci M, Passero V, Stone RA, Smith KJ, Rogers R, *et al*: Adjuvant chemotherapy for stage III colon cancer: Relative dose intensity and survival among veterans. BMC Cancer 15: 62, 2015.
22. Kirshner JJ, Heckler CE, Janelsins MC, Dakhil SR, Hopkins JO, Coles C and Morrow GR: Prevention of pegfilgrastim-induced bone pain: A phase III double-blind placebo-controlled randomized clinical trial of the university of rochester cancer center clinical community oncology program research base. J Clin Oncol 30: 1974-1979, 2012.
23. Kirshner JJ, McDonald MC III, Kruter F, Guinigundo AS, Vanni L, Maxwell CL, Reiner M, Upchurch TE, Garcia J and Morrow PK: NOLAN: A randomized, phase 2 study to estimate the effect of prophylactic naproxen or loratadine vs no prophylactic treatment on bone pain in patients with early-stage breast cancer receiving chemotherapy and pegfilgrastim. Support Care Cancer 26: 1323-1334, 2018.