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ORIGINAL ARTICLE

The Relevance of Docetaxel-related Febrile Neutropenia to Patient-reported Symptoms and the Quality of Life in Japanese, East Asian (Korean, Taiwanese), and Non-East Asian Patients Based on Post-hoc Analyses of Two Randomized Clinical Trials of Docetaxel with and Without Anti-angiogenic Agent in Advanced Non-small Cell Lung Cancer After Progression on Platinum-based Chemotherapy

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ABSTRACT —— ***Objectives.*** The relevance of febrile neutropenia (FN) to patient-reported outcomes (PROs) was examined in Japanese, East Asian (EA), and non-EA patients with stage IV non-small cell lung cancer. ***Materials and Methods.*** PROs were assessed with the Lung Cancer Symptom Scale (LCSS) and EuroQoL-5 Dimensions (EQ-5D) at baseline, every cycle, at discontinuation, and at 30-day follow-up. The time to deterioration (TtD) and mean changes (baseline to treatment completion) in the LCSS total score, average symptom burden index (ASBI), and EQ-5D visual analog scale (VAS) scores were analyzed by the FN status, regardless of the assigned treatment. ***Results.*** For patients with and without FN, the hazard ratios (HRs; 95% confidence interval [CI]) for TtD of the LCSS total, ASBI, and EQ-5D VAS scores were 0.731 (0.469-1.141), 0.621 (0.399-0.967), and 0.802 (0.537-1.199) in Japanese patients, and 0.572 (0.250-1.313), 0.506 (0.228-1.121), and 0.792 (0.350-1.790) in EA patients, respectively, indicating a longer TtD in PROs for patients without FN than for those with FN, while no marked differences by the FN status were noted in non-EA patients. Across the three populations, the mean change in both the LCSS total and EQ-5D VAS scores demonstrated a greater deterioration at treatment completion for patients with FN than for those without FN. ***Conclusions.*** PROs deteriorated more rapidly in patients with FN than in those without FN among Japanese and EA patients but not non-EA patients. Upon treatment completion, PROs were better maintained in patients without FN than in those with FN in all three populations. These findings suggest that active prevention of FN may help maintain PROs during treatment, regardless of ethnic group (ClinicalTrials.gov registration: NCT 01703091 and NCT01168973).

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KEY WORDS —— Docetaxel, Febrile neutropenia, Non-small cell lung cancer, Patient-reported outcome, Quality of life

INTRODUCTION

Lung cancer is the leading cause of cancer-related death in both men and women and is estimated to have caused about 1.76 million deaths worldwide in 2018.[1] Non-small cell lung cancer (NSCLC), a heterogeneous class of tumors, accounts for approximately 80% of all lung cancers,[2] with 5-year survival rates ranging from less than 1% for late stages to 92% for early stages.[3] Most patients with NSCLC present with advanced-stage disease or

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have metastasis at diagnosis, and if untreated, the average survival is between 7 and 11 months.[2] The main treatment goal for patients with advanced-stage NSCLC is to improve the overall survival (OS) and reduce disease-related symptoms while maintaining the overall quality of life (QOL).[4] Recently, several novel agents for NSCLC have been developed, such as epidermal growth factor receptor tyrosine kinase inhibitors, anaplastic lymphoma kinase inhibitors, programmed cell death-1 protein and programmed cell death-ligand 1 inhibitors, and anti-angiogenesis agents.[4] These novel therapies have significantly improved the outcomes of patients with NSCLC; however, they are associated with treatment-related toxicities that necessitate appropriate management of adverse events to maintain the treatment outcomes and patient QOL.[4]

Recently, two multicenter, randomized, double-blind, placebo-controlled clinical trials have reported the efficacy and safety of ramucirumab plus docetaxel (RAM + DTX) in patients with stage IV NSCLC who showed disease progression during or after first-line platinum-based chemotherapy with or without maintenance treatment.[5,6] In the Japanese phase II JVCG trial (ClinicalTrials.gov: NCT01703091), the median OS was 15.15 months (95% confidence interval [CI]: 12.45 to 26.55) with RAM + DTX and 14.65 months (95% CI: 11.93 to 24.44) with placebo plus docetaxel (PLA + DTX; hazard ratio [HR] 0.86, 95% CI: 0.56 to 1.32).[6] In the global phase III REVEL trial (ClinicalTrials.gov: NCT01168973), the median OS was 10.5 months (interquartile range [IQR]: 5.1 to 21.2) with RAM + DTX and 9.1 months (IQR: 4.2 to 18.0) with PLA + DTX (HR 0.86, 95% CI: 0.75 to 0.98, p = 0.023).[5] In both trials, febrile neutropenia (FN), defined as an absolute neutrophil count (ANC) $< 1.0 \times 10^3/\mu l$ ($1.0 \times 10^9/l$) with a single temperature of $\geq 38.3^\circ C$ or a sustained temperature of $\geq 38.0^\circ C$ for more than 1 hour, was one of the most common Grade ≥ 3 adverse events reported (RAM + DTX vs. PLA + DTX: JVCG, 34.2% vs. 19.8%; REVEL, 16.0% vs. 10.0%).[5,6] Neutropenia is a common treatment-related side effect of cytotoxic chemotherapy that may lead to dose reductions or delays that can limit the potential benefits of treatment.[7] FN can also lead to infections and sepsis with potentially fatal consequences.[7,8]

Maintaining patients' QOL during cancer care in advanced NSCLC is a priority.[9] The impact of cultural or ethnic differences on health-related QOL in cancer patients has often been reported.[10-13] In addition, studies have shown that the incidence of DTX-related neutropenia varies among ethnic groups.[14,15] While most cases of drug-induced neutropenia are dose-related and reversible, the impact of neutropenia on patient-reported outcomes (PROs) cannot be underestimated. However, the impact of neutropenia on PROs has only occasionally been examined as a secondary outcome in the context of side effects of chemotherapies.[16] Understanding the impact of DTX-related FN on PROs and whether it varies among different ethnic groups may be valuable when considering treatments associated with a risk of FN.

We herein report our post-hoc analyses of JVCG and REVEL trial data that explored the relevance of DTX-related FN to PROs for symptoms and QOL in Japanese, East Asian (EA; Korean, Taiwanese), and Non-EA patients with NSCLC.

MATERIALS AND METHODS

Study population

Patients in the JVCG trial were enrolled in Japan, and those in the REVEL trial were enrolled in 26 countries, including Korea and Taiwan, in East Asia. In both trials, eligible patients had stage IV NSCLC that had progressed during or after first-line platinum-based chemotherapy regimens. The eligible patients were ≥ 18 (REVEL) or ≥ 20 (JVCG) years, of either sex, with ANC $\geq 1.5 \times 10^3/\mu l$ ($\geq 1.5 \times 10^9/l$), hemoglobin ≥ 10.0 g/dl (≥ 6.2 mmol/*l*), and platelets $\geq 100 \times 10^3/\mu l$ ($\geq 100 \times 10^9/l$) and resolution to Grade ≤ 1 according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 of all clinically significant toxic effects of prior locoregional therapy, surgery, or other anticancer therapy.

Patients were randomly assigned in a 1:1 ratio to receive intravenous RAM (10 mg/kg) + DTX (60 mg/m^2 in JVCG; 75 and 60 mg/m^2 in REVEL) or PLA + DTX on Day 1 of a 3-week (21-day) cycle. Details for both trials have been previously published in the respective primary publications.[5,6] Both trials were conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Guideline for Good Clinical Practice, and the protocol was approved by each participating center's ethical review board. All patients provided their informed consent before receiving treatment.

Post-hoc analyses were carried out for PROs for Japa-

nese patients (N=192) in the JVCG trial, and for EA (Korea [n=62], Taiwan [n=27]) and Non-EA patients (N=1164) in the REVEL trial. The EA population was defined as all patients in the REVEL trial enrolled at study sites in Korea and Taiwan but did not include patients of Korean or Taiwanese ethnicity enrolled at sites other than in Korea and Taiwan. The Non-EA population was defined as patients in the REVEL trial enrolled at study sites around the world outside of Korea, and Taiwan.[17] Patients in all three populations were categorized according to treatment-emergent FN status, regardless of assigned treatment.

Assessments

All patients underwent assessment of PROs for symptoms and QOL using the Lung Cancer Symptom Scale (LCSS) and the three-level version of the EuroQoL-5 Dimensions (EQ-5D-3L). The LCSS is a lung cancer-specific instrument used to evaluate disease-specific symptoms and QOL in lung cancer patients.[18,19] It includes six items focused on lung cancer symptoms (appetite loss, fatigue, cough, dyspnea, hemoptysis, and pain) plus three global QOL items (symptom distress, difficulties with daily activities, and global QOL).[18] Each item is assessed with a 100-mm visual analog scale (VAS). The LCSS total score is calculated as the mean of all nine items, and the average symptom burden index (ASBI) score is calculated as the mean of the six symptom-specific items. A high score for any of the items indicates a high level of symptoms/problems.

The EQ-5D is a standardized instrument to evaluate the QOL applicable to a wide range of health conditions and treatments.[20] It consists of two parts: one that measures the health status with five questions, and the other a VAS.[20] For this analysis, the VAS was used by patients to rate their present health condition, with scores ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

Patients completed the self-administered LCSS and EQ-5D at baseline (within 14 days prior to randomization), around Day 21 in every cycle (including Day 1 of next cycle if no treatment delay), at treatment discontinuation, and at the 30-day follow-up. Any incomplete questionnaires or missing data at each of the assessments were recorded with reasons for incompletion.

The time to deterioration (TtD), defined as the time from randomization to the first ≥15-mm increase from baseline in LCSS[5] and the first ≥15% decrease in EQ-5D VAS,[21] was analyzed for each of the LCSS total, ASBI, and EQ-5D VAS scores by the FN status, regardless of the assigned treatment. The mean change in LCSS total scores and EQ-5D VAS scores from baseline to treatment completion was summarized by the FN status, regardless of the assigned treatment. The use of concomitant medications of granulocyte colony-stimulating factors (G-CSF) / granulocyte (macrophage) colony-stimulating factors (GM-CSF) was permitted during both trials at the discretion of the investigator and was strongly recommended following Grade 3 or 4 neutropenia of >5 days' duration or following any incidence of FN. The G-CSF/GM-CSF used between the treatment start date and the 30-day post-discontinuation follow-up date was summarized by numbers and percentages according to treatment group for each of the three populations.

Statistical analyses

The summary statistics of the LCSS total, ASBI, and EQ-5D VAS scores were calculated for each of the three populations. The LCSS total or the ASBI scores were not calculated if there were one or more missing values.[22] No adjustment or imputation for missing data was performed. The percentage of compliance for LCSS and EQ-5D was calculated as the number of completed assessments divided by the number of expected assessments. Instruments with at least one item completed were considered complete. The TtD and mean change in the LCSS total and EQ-5D VAS scores from baseline to treatment completion were analyzed and summarized by the FN status for each of the three populations. Patients without worsening of symptoms during the study were censored on the date of the last PRO assessment.[22] Kaplan-Meier methods and unadjusted Cox regression models were used to assess TtD, and comparisons were made using a stratified log-rank test.[22] Statistical analyses were performed using the SAS® software program, ver. 9.4 (SAS Institute, Cary, NC, USA). For changes from baseline to treatment completion analyses, only patients who completed questionnaires both at baseline and treatment completion were included. The mean change in the outcomes (LCSS total, ASBI, and EQ-5D VAS scores) from baseline to treatment completion was analyzed with an unadjusted general linear model. The usage rates of G-CSF or GM-CSF and antibiotics were summarized by treatment groups of RAM + DTX and PLA + DTX for each of the three populations.

Table 1. Patient Demographics and Disease Characteristics at Baseline

Baseline Characteristics	Japanese Patients (JVCG Trial) N = 192		EA Patients (REVEL Trial) N = 89		Non-EA Patients (REVEL Trial) N = 1164	
	With FN n = 50	Without FN n = 142	With FN n = 19	Without FN n = 70	With FN n = 143	Without FN n = 1021
Male gender, n (%)	40 (80.0)	97 (68.3)	14 (73.7)	59 (84.3)	101 (70.6)	660 (64.6)
Mean age, years (minimum, maximum)	64.6 (47, 78)	63.0 (27, 78)	60.5 (48, 69)	57.5 (25, 81)	63.3 (41, 79)	60.8 (21, 86)
Histology-non-squamous, n (%)	40 (80.0)	133 (93.7)	12 (63.2)	46 (65.7)	105 (73.4)	749 (74.3)
Histology-squamous, n (%)	10 (20.0)	9 (6.3)	7 (36.8)	24 (34.3)	38 (26.6)	259 (25.7)
ECOG PS = 1, n (%)	27 (54.0)	80 (56.3)	15 (78.9)	51 (72.9)	8647 (60.8)	692 (67.9)
Prior maintenance therapy, yes, n (%)	26 (52.0)	83 (58.5)	1 (5.3)	16 (22.9)	30 (21.0)	231 (22.6)
Prior taxane, n (%)	12 (24.0)	39 (27.5)	3 (15.8)	7 (10.0)	37 (25.9)	255 (25.0)
Prior bevacizumab, n (%)	12 (24.0)	46 (32.4)	0	4 (5.7)	20 (14.0)	156 (15.3)
Best response to platinum (CR/PR/SD), n (%)	45 (90.0)	121 (85.2)	15 (88.2)	55 (83.3)	96 (69.6)	671 (68.8)
Best response to platinum (PD), n (%)	2 (4.0)	16 (11.3)	2 (11.8)	11 (16.7)	42 (30.4)	305 (31.3)

CR, complete response; EA, East Asian; ECOG PS, Eastern Cooperative Oncology Group performance status; FN, febrile neutropenia; PD, progressive disease; PR, partial response; SD, stable disease.

Table 2. Incidence of FN at Baseline, in Each Cycle, and at Follow-up During the Study

Visit, n (%)	Japanese Patients (JVCG Trial) N = 192	EA Patients (REVEL Trial) N = 89	Non-EA Patients (REVEL Trial) N = 1164
1	32 (16.7)	5 (5.6)	85 (7.3)
2	11 (6.3)	4 (5.3)	35 (3.4)
3	2 (1.5)	1 (2.0)	10 (1.3)
4	3 (2.4)	4 (8.5)	8 (1.2)
5	1 (1.1)	2 (5.0)	5 (0.9)
6	1 (1.2)	3 (7.9)	8 (1.6)
7	0	2 (6.7)	3 (0.9)
8	0	1 (4.0)	6 (1.8)
9	1 (1.8)	1 (5.0)	1 (0.4)
10	1 (2.1)	0	1 (0.5)
12	1 (3.2)	0	1 (0.7)
30-day follow-up	3 (1.6)	0	3 (0.3)
Cycle missing	1	0	1
All	50 (26.0)	19 (21.3)	143 (12.3)

EA, East Asian; FN, febrile neutropenia.

RESULTS

Patient disposition and clinical characteristics

A total of 192 Japanese patients in the JVCG trial and 1253 (89 EA and 1164 Non-EA) patients in the REVEL trial were included in this analysis. Baseline demographics and disease characteristics for the two trials by FN status are described in Table 1. The starting dose of DTX was different in each population; DTX was started at 60 mg/m^2 in Japanese patients, which is the approved dose in Japan, and at 75 mg/m^2 in EA (n=65) and non-EA patients. However, owing to a higher rate of FN in EA patients (n=18, 27.7%) than in Non-EA patients (n=143, 12.3%) during the REVEL trial, the protocol was amended, and the starting dose of DTX was reduced from 75 to 60 mg/m^2 for newly enrolled EA patients (n=24), which reduced the rate of FN occurrence in this population to only 1 patient.[5] FN occurred at a higher rate in Japanese patients (26.0%) and EA patients (21.3%) than in Non-EA patients (12.3%). FN occurred over the entire treatment period, but its incidence was highest in the first cycle in all three populations (Table 2).

Patient compliance with LCSS and EQ-5D was generally balanced between patients of each FN status in all

Table 3. Compliance Rates for LCSS and EQ-5D for All Three Populations During the Study

	Japanese Patients (JVCG Trial) N = 192		EA Patients[a] (REVEL Trial) N = 89		Non-EA Patients[b] (REVEL Trial) N = 1164[c]	
Visit, n (%)	LCSS	EQ-5D	LCSS	EQ-5D	LCSS	EQ-5D
Overall	1492 (93.7)	1493 (93.8)	561 (84.2)	562 (84.4)	7301 (82.7)	7346 (83.2)
Baseline	191 (99.5)	192 (100.0)	64 (71.9)	64 (71.9)	978 (84.0)	996 (85.6)
1	179 (93.2)	179 (93.2)	46 (51.7)	47 (52.8)	714 (61.8)	717 (62.1)
2	155 (88.6)	155 (88.6)	70 (93.3)	70 (93.3)	882 (86.8)	894 (88.0)
3	126 (95.5)	126 (95.5)	44 (86.3)	44 (86.3)	665 (89.0)	663 (88.8)
4	113 (91.9)	113 (91.9)	47 (100.0)	47 (100.0)	607 (91.4)	613 (92.3)
5	91 (97.8)	91 (97.8)	37 (92.5)	37 (92.5)	486 (91.4)	488 (91.7)
6	82 (95.3)	82 (95.3)	37 (97.4)	37 (97.4)	428 (87.3)	432 (88.2)
7	68 (97.1)	68 (97.1)	27 (90.0)	27 (90.0)	327 (92.6)	326 (92.4)
8	64 (94.1)	64 (94.1)	25 (100.0)	25 (100.0)	291 (88.7)	289 (88.1)
9	56 (98.2)	56 (98.2)	19 (95.0)	19 (95.0)	226 (90.8)	227 (91.2)
10	43 (89.6)	43 (89.6)	14 (100.0)	14 (100.0)	195 (88.2)	196 (88.7)
Treatment discontinuation	163 (91.6)	163 (91.6)	63 (80.8)	63 (80.8)	569 (63.4)	568 (63.3)

[a] Includes Korean and Taiwanese patients. [b] Excludes Korean and Taiwanese patients. [c] Because compliance rates were calculated as the number of completed assessments divided by the number of expected assessments, the N values (number of expected assessments) for all three populations differed for each cycle. The N values for Japanese patients for both LCSS and EQ-5D were as follows: baseline = 192, Cycle 1 = 192, Cycle 2 = 175, Cycle 3 = 132, Cycle 4 = 123, Cycle 5 = 93, Cycle 6 = 86, Cycle 7 = 70, Cycle 8 = 68, Cycle 9 = 57, Cycle 10 = 48, treatment discontinuation = 178. The N values for EA patients for both LCSS and EQ-5D were as follows: baseline = 89, Cycle 1 = 89, Cycle 2 = 75, Cycle 3 = 51, Cycle 4 = 47, Cycle 5 = 40, Cycle 6 = 38, Cycle 7 = 30, Cycle 8 = 25, Cycle 9 = 20, Cycle 10 = 14, treatment discontinuation = 78. The N values for Non-EA patients for both LCSS and EQ-5D were as follows: baseline = 1164, Cycle 1 = 1155, Cycle 2 = 1016, Cycle 3 = 747, Cycle 4 = 664, Cycle 5 = 532, Cycle 6 = 490, Cycle 7 = 353, Cycle 8 = 328, Cycle 9 = 249, Cycle 10 = 221, treatment discontinuation = 897.

EA, East Asian; EQ-5D, The EuroQoL-5 Dimensions; LCSS, Lung Cancer Symptom Scale.

three populations. Across all assessments, patient compliance with LCSS and EQ-5D by FN status (patients with FN vs. without FN) was approximately 91.5% vs. 94.6% for both tools in Japanese patients, 88.6% vs. 82.8% for LCSS and 88.6% vs. 83.0% for EQ-5D in EA patients, and 82.9% vs. 82.6% for LCSS and 84.0% vs. 83.0% for EQ-5D in Non-EA patients. Table 3 shows the overall compliance rates for all three populations. The baseline compliance rates for LCSS and EQ-5D were 99.5% and 100%, respectively, in Japanese patients; 71.9% for both LCSS and EQ-5D in EA patients; and 84.0% and 85.6%, respectively, in Non-EA patients. Compliance with both LCSS and EQ-5D at the time of discontinuation was 91.6% in Japanese patients, 80.8% in EA patients, and 63.4% and 63.3%, respectively, in Non-EA patients.

TtD

The TtD for the LCSS total, ASBI, and EQ-5D VAS scores was longer for patients without FN than for those with FN among Japanese and EA patients, suggesting that the PROs of patients with FN deteriorated more rapidly than in those without FN. In contrast, for Non-EA patients, there appeared to be no marked difference in the TtD for each PRO (Figure 1, 2). The unadjusted HRs (95% CI) for the TtD of LCSS total, ASBI, and EQ-5D VAS scores of patients with FN vs. without FN were 0.731 (0.469 to 1.141), 0.621 (0.399 to 0.967), and 0.802 (0.537 to 1.199), respectively, in Japanese patients, 0.572 (0.250 to 1.313), 0.506 (0.228 to 1.121), and 0.792 (0.350 to 1.790), respectively, in EA patients, and 0.994 (0.728 to 1.357), 0.977 (0.713 to 1.338), and 1.023 (0.787 to 1.330), respectively, in Non-EA patients. However, except for the ASBI scores in Japanese patients, none of the scores assessed with LCSS total, ASBI, or EQ-5D VAS showed statistically significant differences in the TtD between patients with and without FN in any of the three populations.

Among patients who experienced FN, a greater proportion of Japanese, EA, and Non-EA patients showed PRO deterioration after FN occurrence than before FN occurrence. Deterioration in PROs was shown after FN occurrence in 90.0% of Japanese patients for both LCSS total and EQ-5D VAS scores and in 73.7% and 84.2% of EA patients and 93.7% and 89.5% of Non-EA patients for LCSS total and EQ-5D VAS scores, respectively.

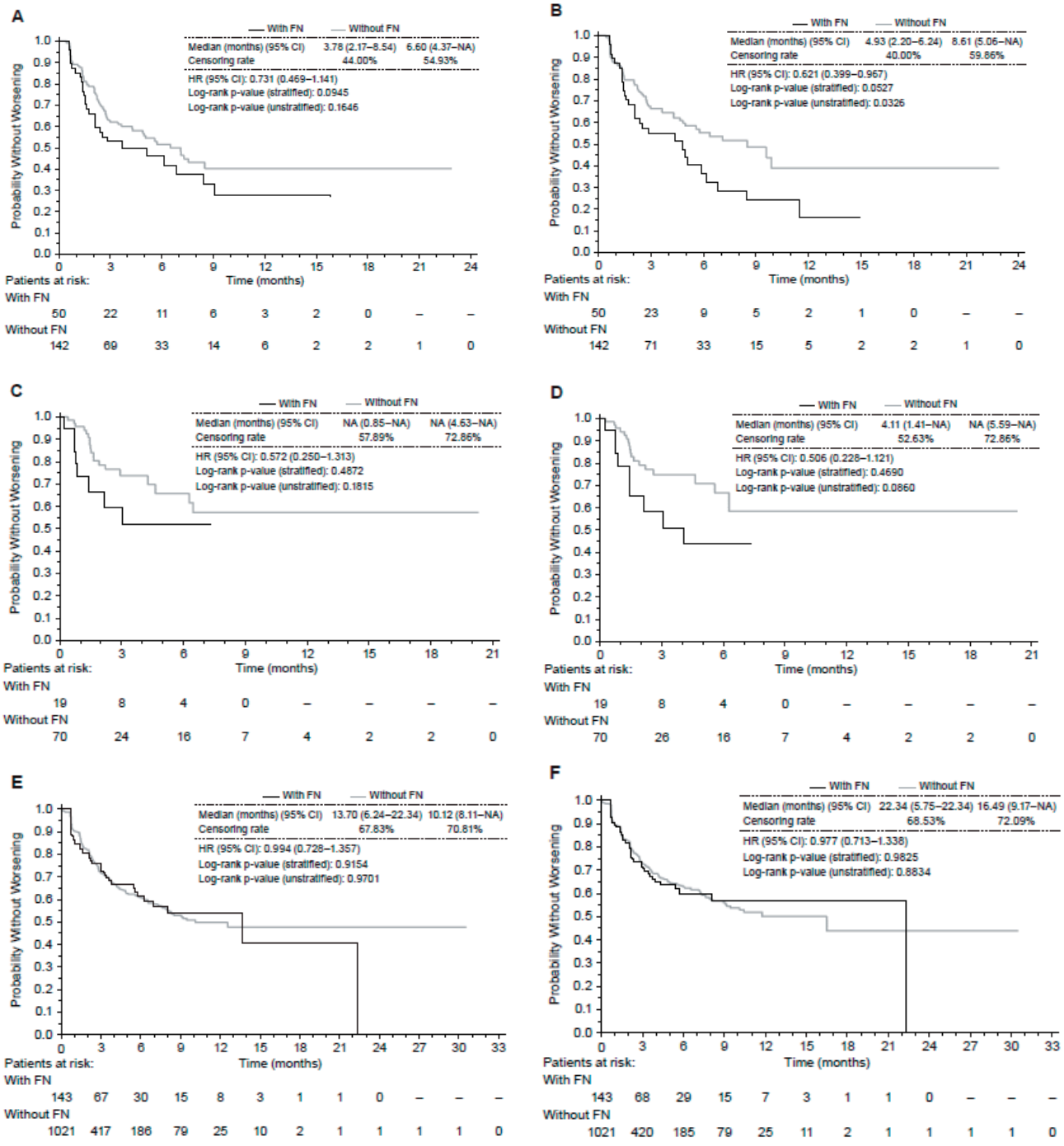

Figure 1. The TtD in the LCSS total and ASBI scores in relation to the treatment-emergent FN status in Japanese patients **(A)** and **(B)**; EA patients **(C)** and **(D)**; and Non-EA patients **(E)** and **(F)**. For LCSS, TtD is the duration from randomization to first ≥15-mm increase from baseline. ASBI, average symptom burden index; CI, confidence interval; EA, East Asian; FN, febrile neutropenia; HR, hazard ratio; LCSS, Lung Cancer Symptom Scale; NA, not assessed; PRO, patient-reported outcome; TtD, time to deterioration.

Change in PROs from baseline to treatment completion

Patients without FN maintained their PROs better than those with FN at treatment completion (Figure 3, 4). At treatment completion, the unadjusted mean change from baseline for LCSS total score was numerically lower in Japanese and EA patients without FN than those with FN and was significantly lower in Non-EA patients without FN than in those with FN (Figure 3).

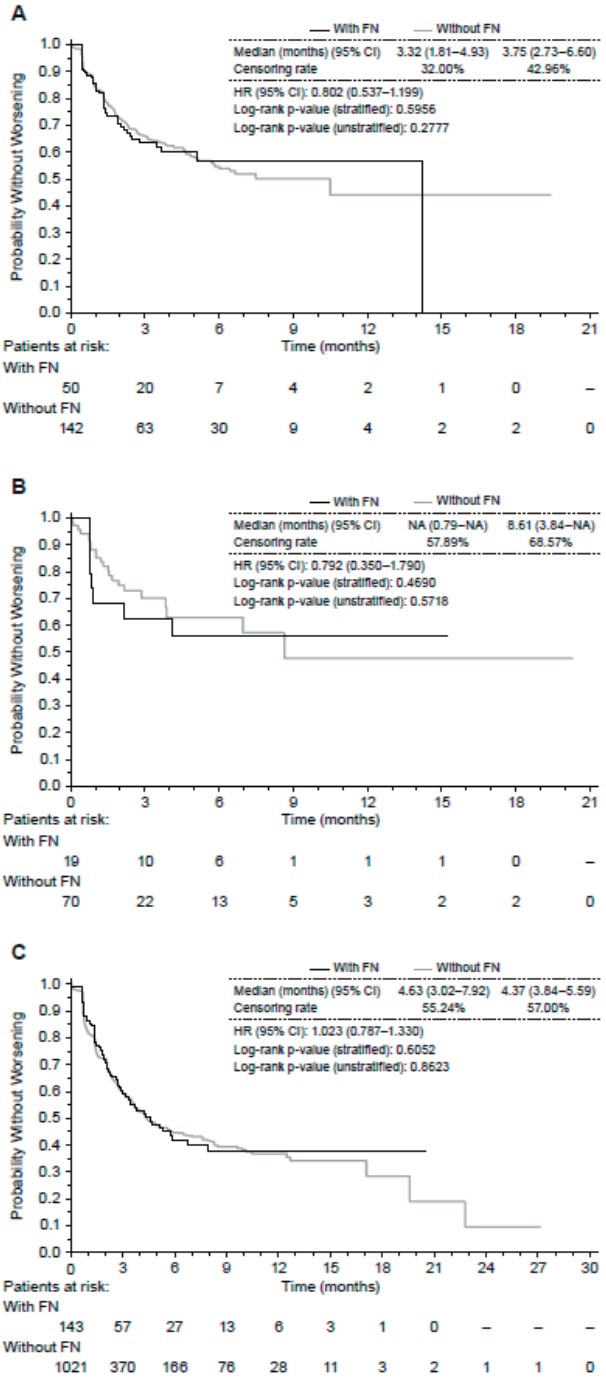

Figure 2. Association between the TtD of the EQ-5D VAS score and the treatment-emergent FN status in Japanese patients **(A)**, EA patients **(B)**, and Non-EA patients **(C)**. For EQ-5D, the TtD is the duration from randomization to the first ≥15% drop from the baseline value. CI, confidence interval; EA, East Asian; EQ-5D, The EuroQoL-5 Dimensions; FN, febrile neutropenia; HR, hazard ratio; NA, not assessed; PRO, patient-reported outcome; TtD, time to deterioration; VAS, visual analog scale.

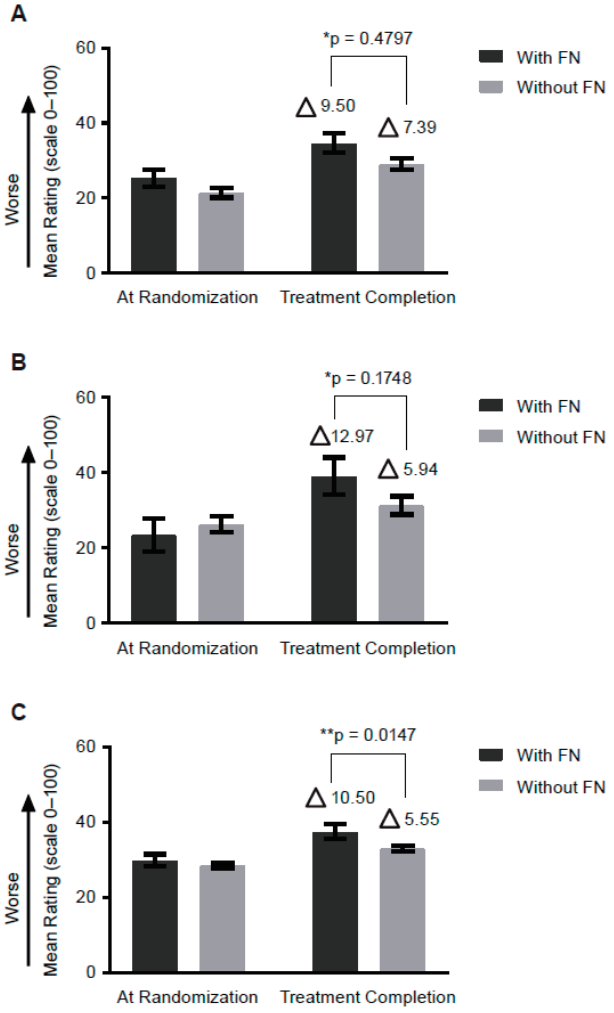

Figure 3. Change in the LCSS total score from randomization to treatment completion in relation to the treatment-emergent FN status in Japanese patients **(A)**, EA patients **(B)**, and Non-EA patients **(C)**. Δ, mean change from baseline with an unadjusted general linear model; vertical bars, SE; *p-value from unadjusted general linear model; **p≤0.05, comparing the difference in mean changes from baseline between patients with and without FN. EA, East Asian; FN, febrile neutropenia; LCSS, Lung Cancer Symptom Scale; SE, standard error.

The unadjusted mean changes from baseline to treatment completion in patients without FN and with FN were 7.39 and 9.50 in Japanese patients (mean difference [95% CI]: 2.11 [−3.33 to 7.54], p=0.4797), 5.94 and 12.97 in EA patients (7.03 [−3.07 to 17.13], p=0.1748), and 5.55 and 10.50 in Non-EA patients (4.96 [0.50 to 0.94], p=0.0147), respectively.

Similarly, the unadjusted mean change in EQ-5D VAS score from baseline to treatment completion was nu-

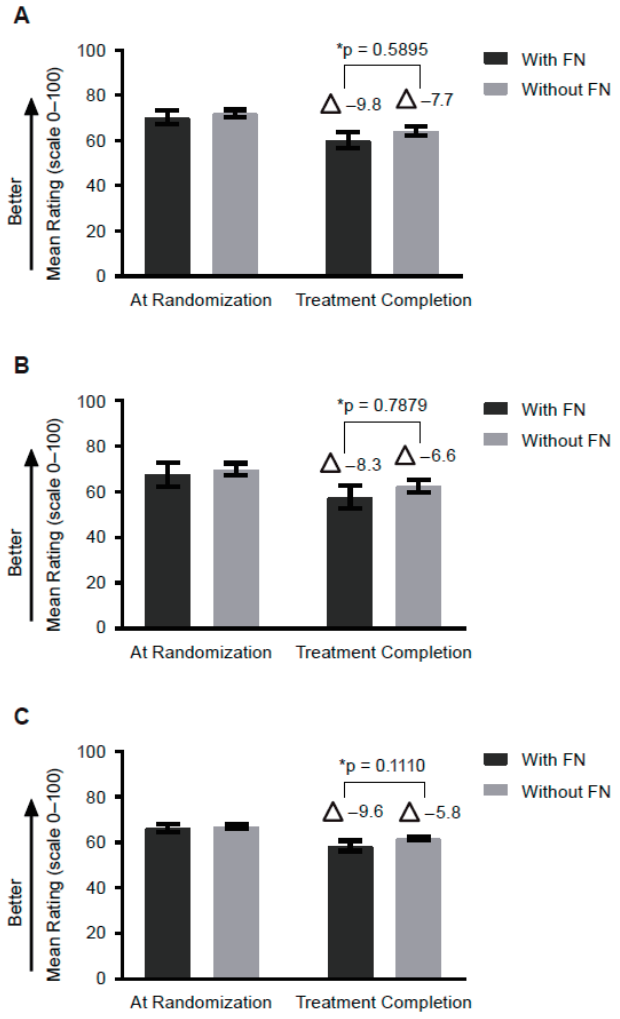

Figure 4. Change in the EQ-5D VAS score from randomization to treatment completion in relation to the treatment-emergent FN status in Japanese patients **(A)**, EA patients **(B)**, and Non-EA patients **(C)**. Δ, mean change from baseline with unadjusted general linear model; vertical bars, SE; *p-value from unadjusted general linear model. EA, East Asian; EQ-5D, The EuroQoL-5 Dimensions; FN, febrile neutropenia; SE, standard error; VAS, visual analog scale.

merically higher in patients without FN than in those with FN in all three patient groups (Figure 4). The unadjusted mean changes from baseline to treatment completion in patients without FN and with FN were −7.7 and −9.8 in Japanese patients (mean difference [95% CI]: −2.0 [−9.1 to 5.0], p=0.5895), −6.6 and −8.3 in EA patients (−1.7 [−13.3 to 9.8], p=0.7879), and −5.8 and −9.6 in Non-EA patients (−3.8 [−8.9 to 1.2], p=0.1110), respectively. None of the differences between patients with and without FN was statistically significant.

Usage rate of G-CSF and antibiotics

In both the JVCG and REVEL trials, G-CSF/GM-CSF and antibiotics were used as concomitant medications for FN. The overall usage rate of G-CSF/GM-CSF was 43% and 39% in JVCG and REVEL, respectively (Table 4). The usage rate of G-CSF/GM-CSF was approximately 43%, 62%, and 37%, and that of antibiotics was 52%, 56%, and 34%, in Japanese, EA, and Non-EA patients, respectively. A very small proportion of patients in all three populations (2%, 1%, and 11% in Japanese, EA, and Non-EA patients, respectively) used G-CSF/GM-CSF as primary prophylaxis. The usage rate of G-CSF/GM-CSF was slightly higher in the RAM + DTX arm than in PLA + DTX in all three populations (23% vs. 20%, 35% vs. 27%, and 20% vs. 18% in Japanese, EA and Non-EA patients, respectively).

DISCUSSION

This is the first study to assess the relevance of DTX-related FN to PROs in three different populations. In this post-hoc analysis of two randomized controlled trials, we examined the relevance of DTX-related FN to PROs in Japanese patients in the JVCG trial and in EA and Non-EA patients in the REVEL trial. The assessment of the TtD with LCSS total, ASBI, and EQ-5D VAS scores suggested a tendency for a more rapid deterioration in PROs in Japanese and EA patients with FN than in those without FN. This finding was not consistent with Non-EA patients, which suggests that the effect of FN on PROs may vary between different ethnic groups. However, this should be considered in light of the possibility of a missed PRO deterioration based on the lower compliance rates in the first cycle for LCSS and EQ-5D among EA (51.7% and 52.8%, respectively) and Non-EA (61.8% and 62.1%, respectively) patients compared with Japanese patients (93.2% for both). An analysis of the changes in PROs from baseline to treatment completion for LCSS total, ASBI, and EQ-5D VAS scores showed greater worsening in PROs in Japanese, EA, and Non-EA patients with FN than in those without FN. These results suggest that patients without FN may be able to maintain better PROs than those with FN during treatment, regardless of ethnic group. In addition, the deterioration in PROs was shown after FN occurrence in most patients who experienced FN in each of the three populations. These results suggest that DTX-related FN can negatively impact the PROs of patients of any eth-

Table 4. Use of G-CSF and Antibiotics

	JVCG: Japanese N = 192		REVEL: EA[a] N = 89		REVEL: Non-EA[b] N = 1164		REVEL: Total (ITT) N = 1253	
	RAM + DTX	PLA + DTX	RAM + DTX	PLA + DTX	RAM + DTX	PLA + DTX	RAM + DTX	PLA + DTX
G-CSF/GM-CSF, total, n (%)	82 (42.7)		55 (61.8)		433 (37.2)		488 (38.9)	
	44 (22.9)	38 (19.8)	31 (34.8)	24 (27.0)	229 (19.7)	204 (17.5)	260 (20.8)	228 (18.2)
1[c]	2 (1.0)	2 (1.0)	1 (1.1)	0	69 (5.9)	59 (5.1)	70 (5.6)	59 (4.7)
2[d]	4 (2.1)	0	1 (1.1)	0	83 (7.1)	82 (7.0)	84 (6.7)	82 (6.5)
Antibiotics, n (%)	57 (29.7)	42 (21.9)	24 (27.0)	26 (29.2)	223 (19.2)	171 (14.7)	247 (19.7)	197 (15.7)

[a] Includes Korean and Taiwanese patients. [b] Excludes Korean and Taiwanese patients. [c] Primary prophylaxis: G-CSF/GM-CSF given prophylactically or non-therapeutically from the first cycle of chemotherapy without confirmation of FN. [d] Secondary prophylaxis: G-CSF/GM-CSF given prophylactically or non-therapeutically in response to occurrence of FN in the prior cycle.

DTX, docetaxel; EA, East Asian; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte (macrophage) colony-stimulating factor; ITT, intent-to-treat; PLA, placebo; RAM, ramucirumab.

nic group, and the impact is expected to be in the QOL and also disease-specific symptoms.

The minimally important difference (MID) is defined as the smallest change in a PRO measure that is perceived by patients as beneficial or that would result in a change in treatment.[21] The MID for LCSS has previously been reported as a 10- to 25-mm change in the VAS.[23] In this study, the magnitude of the changes in the LCSS total score from baseline to treatment completion was ≥10 in patients with FN in EA and Non-EA patients, which was considered to indicate clinically relevant worsening. Estimates of the MID in EQ-5D VAS score for patients with lung cancer suggest that a mean change of ≥7 is clinically relevant.[21] In this study, the magnitude of the changes in the EQ-5D VAS score from baseline to treatment completion was ≥7 in patients with FN in all three populations and in Japanese patients without FN, which was considered clinically relevant worsening.

Previous studies have shown that DTX-related neutropenia is more frequent in Asians than in Caucasians.[14,15,24,25] In this study, the incidence of DTX-related FN was higher in Japanese (26.0%) and EA patients (21.3%) than in Non-EA patients (12.3%). Although FN occurred over the treatment period, the incidence of FN was highest in the first cycle in all three populations. This observation is consistent with a systematic review and meta-analysis showing an increased risk of FN during any cycle of cytotoxic chemotherapy, although the risk was shown to be highest during the first cycle, and dose reductions and delays occurred most frequently in subsequent cycles.[26]

Since 2006, American Society of Clinical Oncology (ASCO) guidelines have recommended primary prophylaxis with G-CSF only when the risk of FN is approximately ≥20%.[27] However, the guidelines have not been consistently followed in clinical practice for various reasons, such as differences between physician experiences, practice setting reimbursement, and the geographical location of care.[28] In the JVCG and REVEL trials, G-CSF administration was inconsistent and left to each physician's discretion. The use of primary and secondary prophylactic G-CSF was 2.1% and 2.1% in the JVCG trial and 10.3% and 13.2% in the REVEL trial, respectively, which showed infrequent primary prophylaxis with G-CSF in these trials. Table 4 shows the usage rate of antibiotics in both trials.

The main limitation of this study was the post-hoc nature of the analyses and the high censoring rate of patients, especially in EA and Non-EA patients, which resulted in inadequate data and potentially insufficient power to establish a firm conclusion. However, the use of three different measures (LCSS total score, ASBI, and EQ-5D VAS) for the assessment of PROs enabled this analysis to explore the relevance of DTX-related FN to PROs from several perspectives. Recent data suggest that other toxicities of chemotherapy may be worsened or prolonged during severe neutropenia or FN.[29] It should be taken into consideration that this worsening of adverse events in the presence of FN may also have a profound effect on the patient QOL. The hypothesis that the prevention of FN may help maintain PROs assumes that deterioration in PROs follows the occurrence of FN and is at least a direct or indirect consequence of FN.

The assumed temporal order is borne out in most, but not all, cases. The extent to which FN is a causal factor

in the deterioration of PROs therefore warrants further exploration.

CONCLUSION

In conclusion, these analyses of the JVCG and REVEL trials showed that the PROs of Japanese and EA (Korea, Taiwan) patients with FN deteriorated more rapidly than patients without FN. This tendency was not found in Non-EA patients. Upon treatment completion, PROs were also significantly better maintained in Non-EA patients without FN than in those with FN. This finding was consistent with the results in Japanese and EA patients. The incidence of FN was highest in the first cycle in all three populations, suggesting that active prevention of FN from the first cycle of treatment with DTX may help maintain PROs during treatment in patients, regardless of ethnic group.

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