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A Pilot Study of Dose-Dense Paclitaxel With Trastuzumab and Lapatinib for Node-negative HER2-Overexpressed Breast Cancer

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Abstract

Treatment of human epidermal growth factor receptor-2 (HER2)-positive breast cancer with dual anti-HER2 therapy has been shown to improve outcomes. In the present pilot phase II study, patients with early-stage HER2-positive breast cancer received adjuvant treatment with dose-dense paclitaxel, trastuzumab, and lapatinib. However, this combination was not feasible because of unexpected toxicity.

Background—Dual anti-HER2 therapy is effective for HER2-amplified breast cancer. Weekly paclitaxel, trastuzumab, and full-dose lapatinib (PTL) is not feasible because of grade 3 diarrhea. We conducted a phase II feasibility study of dose-dense (DD; every other week) PTL (ClinicalTrials.gov identifier, NCT01827163).

Patients and Methods—Eligible patients had HER2-positive breast cancer, tumor size ≤ 3 cm, and negative nodes. Treatment included paclitaxel ($175 \text{ mg/m}^2 \times 4$, every 2 weeks with pegfilgrastim), trastuzumab (4 mg/kg load and then 2 mg/kg weekly), and lapatinib (1000 mg daily). After paclitaxel $\times 4$, trastuzumab (6 mg/kg every 3 weeks) plus lapatinib were continued for 1 year. The primary endpoint was feasibility, defined as (1) $> 80\%$ of patients completing PTL without a dose delay or reduction, (2) grade 3 diarrhea rate $< 20\%$, and (3) cardiac event rate $< 4\%$.

Results—From May 2013 to November 2013, we enrolled 20 of 55 planned patients. The median age was 49 years (range, 34–74 years). One patient had immediate paclitaxel hypersensitivity and was deemed inevaluable. Only 13 of 19 evaluable patients (68%) completed PTL without a dose delay or reduction or unacceptable toxicities. Only 3 of 19 (16%) had grade 3 diarrhea. Rash was frequent, with all grades in 18 of 19 (95%) and grade 3 in 2 of 19 (11%). The study was stopped early because of excess toxicity.

Conclusion—The discontinuation rate during DD PTL was high, owing, in part, to an unexpectedly high incidence of rash. The trial was halted, because the initial discontinuation rate from overall toxicity made it unlikely that full accrual would demonstrate feasibility.

Keywords

ALTTO; Dose-dense chemotherapy; Dose schedule; Drug toxicity; Taxane

Introduction

We previously conducted a trial of dose-dense (DD) doxorubicin and cyclophosphamide (AC) followed by weekly paclitaxel with trastuzumab and lapatinib (PTL) in patients with stage I to III breast cancer with overexpression or amplification of the human epidermal growth factor receptor-2 (HER2) and reported that this combination was not feasible owing to a high rate of grade 3 diarrhea.¹ Specifically, this regimen was not feasible with a lapatinib dose of 1000 mg daily, because all-grade diarrhea was experienced by 88% of patients, with 29% of these patients experiencing grade 3 diarrhea. The study was closed early, because 43% of patients required a lapatinib dose reduction owing to grade 3 or unacceptable grade 2 diarrhea. These findings established key safety data and led to the modification of the PTL arm of the larger phase III adjuvant study, Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO). Other studies have demonstrated similarly high rates of diarrhea with PTL at a lapatinib dose of 1000 mg daily.^{2–4} Additionally, diarrhea was reported to be the dose-limiting toxicity for this combination when administered in the metastatic setting.⁵

Dual targeting of HER2 has been demonstrated to be superior to single-agent anti-HER2 therapy in both the metastatic and the neoadjuvant settings.^{2,3,6–8} The ALTTO study randomized patients to single-agent trastuzumab with taxane versus taxane plus dual anti-HER2 therapy with trastuzumab and lapatinib at a modified dose of 750 mg during the taxane phase. In a pooled analysis of lapatinib usage in the metastatic setting, Crown et al⁹ reported a low incidence of grade 3 diarrhea (< 10%) when lapatinib was combined with paclitaxel administered every 3 weeks at various doses. Both the every-3-week and DD (every-2-week) schedules of paclitaxel administration were associated with a low incidence of diarrhea.¹⁰ We hypothesized that the optimally tolerated dose of lapatinib 1000 mg daily with trastuzumab could be administered with DD paclitaxel.¹¹ To identify alternate, tolerable dual anti-HER2 regimens in the adjuvant treatment of breast cancer, we conducted a phase II study of trastuzumab plus lapatinib at the full dose of 1000 mg with DD paclitaxel.

Patients and Methods

The present study was a phase II trial of adjuvant chemotherapy with DD paclitaxel with trastuzumab and lapatinib. Patients received endocrine therapy and radiation, as appropriate. The primary objective was to determine the feasibility of this regimen in patients with lymph node-negative HER2-overexpressed/amplified breast cancer with a primary tumor size of ≤ 3 cm. Feasibility was defined as completion of the PTL portion of the regimen without a dose delay or reduction or grade ≥ 3 QTc prolongation. Given that > 85% of patients enrolled on standard adjuvant trials complete the intended study regimens without a dose delay or reduction,^{10,12–14} we planned to accrue 55 patients to our study. With this sample size, we

would have had 90% power and 5% type I error to discriminate between true completion rates of 65% and 80%. A completion rate of 65% would indicate that this regimen was not feasible. Thus, the regimen would be considered feasible if 42 patients completed the DD PTL portion without a dose delay or reduction.

With regard to safety, we incorporated 2 early termination rules for gastrointestinal and cardiac toxicity. The allowable rate of grade 3 diarrhea was set at 20%, and the unacceptable rate was set at 40%. Assessment of the diarrhea rate was preplanned after enrollment of every 10th patient based on repeat significance testing. The probability of stopping the trial for a true diarrhea rate of 20% and 40% was 12% and 97%, respectively. With regard to the second stopping rule, the allowable incidence of cardiac events was set at 4%, a rate consistent with reported adjuvant trastuzumab trials.^{15–17} A cardiac event was defined as (1) cardiac death or (2) symptomatic congestive heart failure (CHF) defined as dyspnea with normal activity or at rest and an absolute decline in the left ventricular ejection fraction (LVEF) by > 10% to < 50%. The probability of stopping the trial for a true cardiac event rate of 4% and 8% was 38% and 83%, respectively. The secondary endpoints included the assessment of other toxicities and an exploratory analysis of serial cardiac biomarkers, including troponin I, B-type natriuretic peptide, and neuregulin-1 β .

Patients

Eligible patients had histologically confirmed breast adenocarcinoma measuring ≥ 3.0 cm with HER2 immunohistochemistry (IHC) 3+ or fluorescent in situ hybridization (FISH) amplification (ratio ≥ 2.0), and no nodal involvement. Hematologic parameters included an absolute neutrophil count $\geq 1000/\mu\text{L}$, platelet count $\geq 100,000/\mu\text{L}$, normal total bilirubin, and transaminases < 2.5 of the upper limit of normal. A normal LVEF of $\geq 50\%$ on the echocardiogram (ECG) or multigated acquisition scan was required. Patients could not concomitantly use CYP3A4 inducers or inhibitors or drugs that can prolong the QTc interval. Patients with a known history of unstable angina, myocardial infarction, CHF, or serious medical illnesses were excluded. The institutional review board at Memorial Sloan Kettering Cancer Center approved the present study. Eligible patients were enrolled after providing written informed consent to participate.

Treatment

Treatment consisted of paclitaxel $175 \text{ mg}/\text{m}^2 \times 4$ intravenously (IV) every 2 weeks, with IV trastuzumab (4 mg/kg load, 2 mg/kg weekly during chemotherapy, and then 6 mg/kg every third week afterward) and lapatinib (1000 mg orally daily). Filgrastim or pegfilgrastim was given during the paclitaxel phase. Both anti-HER2 therapies were given for 1 year (Figure 1).

Evaluations During Therapy

Evaluations, including complete blood count, liver function test, metabolic panel with potassium and magnesium, electrocardiograms, ECGs, and cardiac biomarkers were obtained at the time points outlined in Figure 1.

Toxicity Assessments and Dose Modifications

The toxicities were assessed using the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0. For paclitaxel, patients who experienced neutropenic fever and/or grade 3 or 4 nonhematologic toxicity had subsequent doses reduced by 25%. Only 1 dose reduction was allowed. Patients with grade 4 hypersensitivity reactions were removed from study. Dose modifications for trastuzumab were not permitted. With lapatinib, patients who experienced grade 3 or unacceptable grade ≤ 2 toxicity related to lapatinib had the drug withheld for 21 days until improvement to grade ≤ 1 . One lapatinib dose reduction (1000 mg to 750 mg) was allowed. A second grade 3 event mandated withdrawal from the present study. The guidelines for the management of lapatinib-related diarrhea and rash are listed in Table 1.

Results

From May 2013 through November 2013, 20 of 55 planned patients were enrolled. All patients had early-stage breast cancer that was HER2 IHC 3+ or FISH-amplified, or both. The patient characteristics are listed in Table 2. Overall, 17 of the 20 patients (85%) had estrogen receptor-positive tumors. The tumor stage included T1a in 20%, T1b in 30%, T1c in 40%, and T2 ≤ 3 cm in 10%. One patient immediately withdrew from study because of a paclitaxel hypersensitivity reaction and was deemed inevaluable. Of the 19 evaluable patients, 13 (68%) completed the PTL phase without any dose delay or reduction and 6 (32%) withdrew because of toxicities, 2 of whom also required lapatinib dose reduction during the PTL phase (Figure 2). Most of the toxicities were unanticipated rash, and, accordingly, the study was stopped early. Additionally, 4 patients required a lapatinib dose reduction during the trastuzumab and lapatinib phase, after completing the PTL portion of the study (Table 3). Overall, 6 patients (32%) required a lapatinib dose reduction.

Diarrhea

Of the 19 evaluable patients, 16 (84%) experienced diarrhea: 3 (16%) had grade 3, 5 (26%) had grade 2, and 8 (42%) had grade 1 events. The onset of diarrhea for all patients, except for 1, was within the first week of treatment. One patient experienced diarrhea starting the second week. Three patients (16%) discontinued the study treatment during the PTL phase because of grade 3 diarrhea. Of these 3 patients, 2 experienced grade 3 diarrhea during cycles 1 and 3, respectively, and withdrew before the dose reduction of lapatinib. The third patient developed grade 3 diarrhea during cycle 1. After it had improved to grade 1, the lapatinib dose was reduced. However, grade 3 diarrhea recurred during cycle 4, and the patient withdrew from the study.

Rash

The development of rash was almost universal, occurring in 18 of the 19 evaluable patients (95%). Rash occurred within the first week of treatment in 15 patients (78%). The grade 1, 2, and 3 event rates for all rashes were 47%, 37%, and 11%, respectively. When stratified by the type of rash, the grade 1, 2, and 3 event rates for acneiform rash were 32%, 21%, and 0%, respectively. The grade 1, 2, and 3 event rates for maculopapular rash were 5%, 11%, and 0%, respectively, and 1 patient (5%) developed grade 2 pustular rash. Two patients

withdrew from study during the PTL phase because of grade 2 and 3 rashes, respectively (Figure 2). One of these patients developed a grade 2 maculopapular rash on the trunk, chest, face, and scalp during cycle 1, within the first week of treatment. She was treated with topical clindamycin and both topical and oral steroids. Her rash improved but recurred after the second paclitaxel dose, and she subsequently withdrew from study. The second patient developed a grade 3 acneiform rash during cycle 1, within the first week of treatment. She was treated with oral antibiotics and topical steroids. The rash improved to grade 2 but persisted after the second paclitaxel dose, and she withdrew from the study.

Nonhematologic and Hematologic Toxicities

The nonhematologic and hematologic toxicities are summarized in Table 4. An unexpectedly high rate of rash occurred, as discussed in the previous section.

Hospitalizations

Of the 19 evaluable patients, 2 (11%) required hospitalization. The lapatinib dose was reduced during the PTL phase for 1 patient who was hospitalized for acute kidney injury due to prerenal azotemia and dehydration, unrelated to the study drugs. Her kidney function improved with intravenous hydration, and the lapatinib dose was reduced with the fourth paclitaxel dose. She experienced grade 1 diarrhea only during the first week of study treatment, and this resolved with antidiarrheal agents. After completing the PTL phase with a lapatinib dose reduction, she was again hospitalized for hypertensive urgency and acute kidney injury. Renal biopsy revealed focal necrotizing crescentic glomerulonephritis, and she was also found to have a monoclonal gammopathy. Study treatment was subsequently discontinued. She was treated with cyclophosphamide and steroids for her kidney disease and referred to the hematology section. Overall, her complicated course was attributed to the monoclonal gammopathy.

A second patient was hospitalized after completing the PTL phase because of lapatinib-induced hepatotoxicity. At 8 weeks after completing the paclitaxel phase, this patient was hospitalized for grade 4 aspartate aminotransferase and alanine aminotransferase elevation while taking lapatinib and trastuzumab. Lapatinib was withheld, and liver biopsy revealed acute hepatitis with macrophage and eosinophilic infiltrate, consistent with drug-induced injury.¹⁸ The patient stopped the study treatment, and her hepatic function returned to normal with oral steroid treatment.

Cardiac Outcomes

No cardiac events developed. The median LVEF values were as follows: at baseline, 66% (range, 58%–78%; n = 20); at month 2, 65% (range, 58%–74%; n = 13); at month 6, 63% (range, 59%–68%; n = 6). One patient had an asymptomatic LVEF decline > 10% (from 78% to 60%) after completing the PTL phase. The study treatment was held, and a repeat ECG 3 days later showed a LVEF of 71%, and treatment was resumed.

Discussion

Our phase II study of DD PTL did not establish the feasibility of using a lapatinib dose of 1000 mg daily. Although the incidence of grade 3 diarrhea was < 20%, the incidence of rash was high, with an incidence for all grades of 95% (grade 1, 53%; grade 2, 37%; and grade 3, 5%). During the PTL phase, 32% of patients withdrew. Also, overall, 32% required a lapatinib dose delay or reduction at any point in the study treatment. Accordingly, the study was closed early.

The high incidence of rash was unexpected. In our previously reported study of DD AC followed by weekly paclitaxel with trastuzumab and lapatinib, the incidence of rash was lower, with an incidence for all grades of 27% (grade 1, 18%; grade 2, 5%; and grade 3, 4%).¹ However, the findings in our present study were similar to those previously reported in a pilot neoadjuvant trial of lapatinib with nab-paclitaxel given every 3 weeks.¹⁹ In that study, the overall incidence of all-grade rash was 67% (grade 1, 27%; grade 2, 37%; and grade 3, 3%) with a lapatinib dose of 1000 mg daily and an every-3-week taxane schedule. Consistently, in a meta-analysis of 9 clinical trials, which included patients with advanced or metastatic cancer, Lacouture et al²⁰ reported an event rate of 47% and 50% of all-grade rash in patients receiving lapatinib mono-therapy or lapatinib plus paclitaxel, respectively. The lapatinib dose ranged from 1000 mg to 1500 mg, and the development of a dermatologic complication occurred early in the course of treatment. Similarly, in our study, rash appeared within the first week of treatment in almost all patients who experienced this toxicity. Other studies have also reported early onset of lapatinib-associated rash. In a post hoc analysis of the Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation trial, the median onset of rash in patients receiving lapatinib alone or combined with trastuzumab followed by paclitaxel was 2 weeks (interquartile range, 1.1–4.2 weeks).²¹ The incidence of all-grade rash in patients receiving lapatinib and trastuzumab followed by paclitaxel was 61.2%. In another phase III study of patients with HER2-overexpressing advanced or metastatic breast cancer, the event rate for all-grade rash was 43% in patients taking lapatinib 1500 mg daily with paclitaxel 175 mg/m² every 3 weeks versus 21% in the placebo arm.²² Several other studies have also reported a rash incidence in excess of 40% in patients receiving lapatinib plus a taxane.^{5,23–26} Although rash is a commonly reported adverse event associated with lapatinib, it appears that the schedule of the coadministered taxane might have an influence on the incidence and severity of this toxicity. In our study, we observed a greater incidence of rash with lapatinib and paclitaxel given every 2 weeks (DD) compared with the reported incidence using the weekly paclitaxel schedule.¹

The mechanisms of lapatinib-associated rash are not well understood and appear to be slightly different from the dermatologic reactions associated with other epidermal growth factor receptor (EGFR) inhibitors. Lapatinib is an orally bioavailable, small molecule, dual tyrosine kinase inhibitor of EGFR and HER2. Compared with other EGFR inhibitors, dual EGFR/HER2 inhibition with lapatinib has been associated with a lower incidence of rash.²⁷ Importantly, lapatinib-associated rash has not been shown to be a surrogate of clinical efficacy, unlike rash associated with single EGFR inhibitors.²⁸ Additionally, the distribution of lapatinib-associated rash is distinct—typically involving the trunk and sparing the face.^{20,29} Single inhibitors of EGFR are associated with a more inflammatory, pruritic rash

often involving the face and scalp. The underlying mechanisms of these distinct rashes appear to involve differential effects on keratinocyte proliferation and local inflammation in the skin.²⁷ In a tissue-based study of patients taking either single EGFR inhibitors or dual EGFR/HER2 inhibitors, Nardone et al²⁷ reported increased expression of phospho-AKT and decreased expression of Ki-67 and p27 in skin biopsies from patients receiving dual EGFR/HER2 inhibition with lapatinib compared with single EGFR inhibition. These findings suggest a lower degree of dermal turnover in EGFR/HER2 inhibitor-associated rash. Furthermore, decreased inflammatory cell infiltrate was noted in biopsy specimens of lapatinib-associated rash compared with rash associated with single EGFR inhibition.

In terms of diarrhea, we report an all-grade event rate of 84%, with a grade 3 event rate of 16%. This finding is consistent with 2 phase I studies of lapatinib with a taxane. The incidence of all-grade diarrhea was 82% in the EGF10009 trial (lapatinib at 1250–1500 mg daily with paclitaxel at 135–225 mg/m² every 3 weeks or 80 mg/m² weekly) and 71% in the EGF10021 trial (lapatinib at 1000–1500 mg daily and docetaxel 50–75 mg/m² every 3 weeks).⁹ The incidence of grade 3 diarrhea in the EGF10009 trial was greater in patients who received lapatinib plus paclitaxel given weekly (50%) than in those who received paclitaxel every 3 weeks (7%). However, when combined with trastuzumab and paclitaxel given weekly, we have previously demonstrated that lapatinib at 1000 mg is not feasible because of excessive grade 3 diarrhea (29%).¹ Although the incidence of grade 3 diarrhea was lower with the every-other-week schedule, overall toxicity remained excessive, with an unexpectedly high incidence of rash as discussed.

No cardiac events, as defined, occurred within the present study. Given this and the small patient number, we decided not to analyze the cardiac biomarkers.

Conclusion

The present pilot study has demonstrated an unexpected toxicity for DD paclitaxel, trastuzumab, and full-dose lapatinib: a high rate of dose-limiting rash. The mechanism of this toxicity should be explored to facilitate optimization of this active agent. Schedule and dose modifications might enable the delivery of lapatinib in a more effective, but less toxic, fashion.

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Clinical Practice Points

- Given the findings from the ALTTO study, our study addressed the important question of whether administration of full-dose lapatinib with trastuzumab is feasible with an alternate chemotherapy schedule.
- Several factors could have contributed to the negative findings from ALTTO, including the lapatinib dose and adherence to therapy.
- Thus, delivery of lapatinib in a more effective, but less toxic, fashion represents an important therapeutic question.
- We conducted a pilot study of an every-2-week (DD) schedule of paclitaxel with trastuzumab and lapatinib 1000 mg for patients with node-negative HER2-amplified breast cancer.
- However, our study did not establish feasibility using a DD paclitaxel schedule.
- Although the incidence of grade 3 diarrhea was acceptable according to the study design, the incidence of rash was unexpectedly high, and the study was closed early.
- Thus, full-dose lapatinib combined with trastuzumab and paclitaxel delivered using a DD schedule was not a clinically feasible combination because of the toxicity.
- These findings help to address whether alternate schedules and dosing of dual anti-HER2 therapy with lapatinib should be further investigated.
- Although subpar drug dosing might have contributed to the negative findings from the ALTTO study, our study has demonstrated that a feasible delivery schedule with lapatinib remains elusive.

Figure 1. Treatment Schema. Complete Blood Count Every 2 Weeks During Paclitaxel, Trastuzumab, and Lapatinib (PTL); Liver Function Test Every 2 Weeks During PTL and Every 3 to 6 Weeks During Trastuzumab and Lapatinib; Magnesium and Potassium Levels Every 2 Weeks During PTL and Every 3 to 6 Weeks During Trastuzumab and Lapatinib; Cardiac Biomarkers Including Troponin I, B-natriuretic Peptide, and Neuregulin-1 β Every 2 Weeks During PTL Phase (Before and After Infusion) and at Months 6, 9, and 18; Electrocardiogram (EKG) and Multigated Acquisition Scan at Baseline and Months 2, 6, 9, and 18
Abbreviation: ECHO = echocardiogram.

Figure 2. Consolidated Standards of Reporting Trials Diagram

Abbreviations: G = grade; L = lapatinib; PTL = paclitaxel, trastuzumab, and lapatinib; T = trastuzumab.

Table 1

Protocol-Defined Lapatinib Dose Reduction (Starting Dose, 1000 mg Daily)

Grade	Management	Dose Reduction
Diarrhea		
1	None	None
2	Loperamide at first onset	None; if unacceptable, hold 21 days, resume same dose ^a
>3	Loperamide at first onset	Hold 21 days until grade <1, resume at 750 mg daily ^b
Rash		
1	None	None
2	Minocycline, topical tetracycline, or clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course)	None; if unacceptable, hold 21 days, resume same dose ^a
>3	Same as above	Hold 21 days until grade <1, resume at 750 mg daily ^b

^a If the dose was held previously for grade 2 toxicity and the grade 2 event recurred, the drug could be withheld 21 days and reduced to 750 mg daily.

^b Only 1 dose reduction from 1000 mg to 750 mg daily was allowed; if the grade 3 event occurred again at a dose of 750 mg, lapatinib was held and patient taken off the study.

Table 2

Patient Characteristics (n = 20)

Characteristic	n (%)
Age (years)	
Median	49
Range	34–74
Age group (years)	
<40	4 (20)
40–49	7 (35)
50–59	2 (10)
60–69	5 (25)
70	2 (10)
Tumor stage/size	
T1a (>0.1–0.5 cm)	4 (20)
T1b (>0.5–1 cm)	6 (30)
T1c (>1–2 cm)	8 (40)
T2 (>2–3 cm) ^a	2 (10)
No involved nodes (n)	20 (100)
Hormone receptor status	
ER+/PR+	15 (75)
ER+/PR–	2 (10)
ER–/PR+	0 (0)
ER–/PR–	3 (15)
Surgical treatment	
Lumpectomy	16 (80)
MRM	4 (20)
Radiation treatment	
Breast/chest	8 (40)
Left sided	3/8 (38)
Right sided	5/8 (63)
Bilateral	0/8 (0)

Abbreviations: ER = estrogen receptor; PR = progesterone receptor; IHC = immunohistochemistry; MRM = modified radical mastectomy.

^aT2 tumors > 3 cm were excluded.

Table 3

Patients With Lapatinib Dose Reductions (1000 mg Reduced to 750 mg Daily; 6 of 19 Evaluable Patients; 32%)

Toxicity	Patients (n)	Treatment
Grade 3 diarrhea	1/19 (5)	Cycle 4 PTL
Grade 2 rash (unacceptable)	1/19 (5)	During TL
Grade 2 bilirubin	2/19 (10)	During TL
Grade 2 ALT	1/19 (5)	During TL
Grade 3 dehydration	1/19 (5)	Cycle 4 of PTL

Data in parentheses are percentages.

Abbreviations: ALT = alanine aminotransferase; PTL = paclitaxel, trastuzumab, full-dose lapatinib; TL = trastuzumab, lapatinib.

Table 4

Hematologic and Nonhematologic Toxicities (n = 19)

Toxicity	Grade			
	1	2	3	4
Febrile neutropenia	0	0	0	0
Leukopenia	6 (24)	2 (11)	0	0
Neutropenia	0	0	0	0
Anemia	12 (63)	3 (16)	1 (5)	0
Thrombocytopenia	3 (16)	0	0	0
Diarrhea	8 (42)	5 (26)	3 (16)	0
Rash	9 (47)	7 (37)	2 (11)	0
Acneiform rash	6 (32)	4 (21)	0	0
Maculopapular rash	1 (5)	2 (11)	0	0
Pustular rash	0	1 (5)	0	0
Pruritus	3 (16)	1 (5)	0	0
Fatigue	8 (42)	7 (37)	0	0
Fever without neutropenia	5 (26)	1 (5)	0	0
Nausea	8 (42)	1 (5)	0	0
Emesis	1 (5)	1 (5)	0	0
Dyspepsia	5 (26)	2 (11)	0	0
Mucositis	6 (32)	1 (5)	0	0
Constipation	2 (11)	0	0	0
Headache	3 (16)	1 (5)	0	0
Dizziness	3 (16)	1 (5)	0	0
Dyspnea	3 (16)	0	0	0
Neuropathy (sensory)	12 (63)	1 (5)	0	0
Nail changes	3 (16)	0	0	0
Pain (arthralgia)	4 (21)	1 (5)	0	0
AST	11 (58)	0	0	1 (5)
ALT	10 (53)	3 (16)	0	1 (5)

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Toxicity	Grade			
	1	2	3	4
Alkaline phosphatase	13 (68)	0	0	0
Bilirubin	1 (5)	3 (16)	0	0

Data presented as n (%).

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase.