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A phase 2 study of pracinostat combined with ruxolitinib in patients with myelofibrosis

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Abstract

Although ruxolitinib improves symptoms and splenomegaly in patients with advanced myelofibrosis, whether this agent is truly disease-modifying remains unclear. Histone deacetylase inhibitors (HDACi) down-regulate JAK2 via interference with chaperone function. Pracinostat, a pan-HDACi, has modest single-agent activity in myelofibrosis. We conducted a single-institution, phase 2, investigator-initiated trial of ruxolitinib plus pracinostat (begun after 12 weeks of ruxolitinib) in 25 patients with myelofibrosis, of whom 20 received both agents. Sixteen (80%) patients had objective responses (all “clinical improvement”). The rate of spleen response (by palpation) was 74%, and that of symptom response 80%. Most responses occurred prior to pracinostat initiation. Three patients experienced improvement in bone marrow fibrosis, and one a near-complete molecular response after two years on study treatment. All patients discontinued pracinostat and are currently off-study. Pracinostat interruptions and dose reductions were frequent, often due to worsening anemia. These findings do not support continued development of pracinostat in myelofibrosis.

Keywords

myelofibrosis; JAK2 inhibitors; HDAC inhibitors; rational combinations; targeted therapies

Introduction

The Janus kinase 1/2 (JAK1/2) inhibitor, ruxolitinib, first licensed in 2011 for the treatment of myeloproliferative neoplasm (MPN)-associated myelofibrosis (MF), remains the only agent to have received regulatory approval for this disease.[1] The most pronounced benefits of ruxolitinib in MF are reduction in splenomegaly and amelioration of symptoms, and the drug broadly suppresses cytokines, the levels of many of which are increased in patients

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with MF.[2] Ruxolitinib was approved based on the results of the pivotal COMFORT trials conducted in patients with intermediate-2 or high risk MF, and long-term follow-up shows a survival advantage for the ruxolitinib-treated patients in these trials, despite crossover.[3] However, despite the survival benefit seen with ruxolitinib, controversy persists over whether or not this drug is truly disease-modifying, in large part because of the its rather modest effects on bone marrow fibrosis and driver mutation allele burden.[4] Indeed, it has been proposed that the improvement in survival with ruxolitinib could potentially be attributed to indirect effects, such as improved weight, appetite, energy level and overall well-being.[5] The emergence of clinical resistance to ruxolitinib is also of concern: in the COMFORT trials, the median duration of spleen response was about 3 years,[6, 7] and spleen responses to ruxolitinib have been shown to correlate with survival.[8, 9] One major mechanism of therapeutic resistance to JAK2 inhibition is the phenomenon of JAK2 inhibitor "persistence", where JAK2 is activated in trans via heterodimerization with other members of the JAK family despite the presence of a JAK2 inhibitor, such as ruxolitinib.[10] For all these reasons, there has been considerable interest in developing rational, ruxolitinib-based combinations for patients with MF, in hopes of altering the underlying disease biology, extending ruxolitinib's survival benefit, and circumventing resistance.

Histone deacetylase inhibitors (HDACi) exert pleiotropic effects selectively in transformed cells, that include promoting a more open chromatin configuration that favors gene transcription, reactive oxygen species (ROS) generation and induction of DNA damage, inhibition of DNA repair, induction of the endogenous cyclin-dependent kinase (CDK) inhibitor p21, and disruption of chaperone function via acetylation of heat shock protein 90 (HSP90), among many other actions (reviewed in ref.[11]). Through the last mechanism, HDACi have been shown to down-regulate several oncoproteins of critical importance in leukemogenesis, including JAK2.[12] Several non-canonical actions of *JAK2*^{V617F} that broadly impact gene expression through epigenetic mechanisms, such as phosphorylation of histone H3[13] and the arginine methyltransferase PRMT5,[14] provide further support for studying histone modifying drugs in MPN. Inhibitors of HSP90 have also been shown to degrade JAK2 and overcome JAK2 inhibitor persistence,[15] but this class of agents has been difficult to develop for clinical use to date. In contrast, several HDACi are approved for the treatment of T-lymphoid and plasma cell malignancies. A number of HDACi have been tested in clinical trials in MPN and displayed promising single-agent activity (reviewed in ref.[16]). Preclinical studies have demonstrated clear evidence of synergism between JAK2 inhibitors and HDACi against MPN cell lines and primary cells, both *in vitro* and *in vivo*. [17–19]

Pracinostat (MEI Pharma, San Diego, CA; Helsinn Group, Lugano, Switzerland;) is an orally available inhibitor of class I histone deacetylases currently in phase 3 of clinical development for acute myeloid leukemia in combination with azacitidine,[20] for which indication it enjoys "breakthrough" designation from the Food and Drug Administration (FDA). We previously conducted a phase 2 study of pracinostat, administered at a dose of 60 mg every other day for three out of every four weeks, in 22 patients with MF.[21] Eight (36%) patients had clinical benefit, with six (27%) experiencing spleen shrinkage. Two (9%) patients had International Working Group (2006)-defined[22] clinical improvement (CI) in anemia. Based upon these single-agent data and the preclinical rationale and synergism

discussed above, we conducted a phase 2 clinical trial of the combination of ruxolitinib and pracinostat in patients with MF (clinicaltrials.gov identifier NCT02267278).

Methods

This was a phase 2, investigator-initiated, single-institution study in adult patients with primary MF (PMF), post-polycythemia vera MF (post-PV MF) or post-essential thrombocythemia MF (post-ET MF). Key eligibility criteria included the presence of palpable splenomegaly (≥5 cm below the left costal margin), an absolute neutrophil count (ANC) $\geq 1 \times 10^9$/L and a platelet count $\geq 50 \times 10^9$/L. Patients could be treatment-naïve or previously treated; if the former, patients had to have intermediate-1, intermediate-2 or high risk disease according to the International Prognostic Scoring System (IPSS).[23] A corrected QT interval ≤470 milliseconds was required. Prior JAK inhibitor therapy was not permitted, except for ruxolitinib for <3 months' duration and ongoing. Ruxolitinib was administered twice daily, continuously, in 28-day cycles and the starting dose was based on the platelet count, per the US prescribing information; the starting dose of pracinostat was 60 mg every other day for three out of every four weeks. Ruxolitinib was administered alone in the first 3 cycles, i.e., for the first 12 weeks, with pracinostat added on cycle 4, day 1. This was in order to avoid any added toxicity from pracinostat during the period of maximum symptomatic benefit from ruxolitinib. The primary endpoint of the study was the overall response rate (ORR), i.e., the proportion of patients achieving complete response (CR), partial response (PR) or CI according to the 2013 criteria of the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT).[24] Response assessments occurred after cycle 3 and cycle 6, and every six cycles, thereafter. Bone marrow biopsies were required after 6 and 12 cycles of therapy, and after that per the discretion of the treating physician. The MPN Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) questionnaire[25] was administered every cycle in cycles 1 through 7, and every 3 cycles after that. Organomegaly was assessed by palpation. The study planned to accrue 25 patients. The method of Thall, Simon and Estey[26] was used for futility and toxicity moitoring. The study was approved by the MD Anderson Cancer Center (MDACC) Institutional Review Board (IRB), and all patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The full study protocol is available in the Supplementary Appendix. Pracinostat was provided by MEI Pharma, while ruxolitinib was obtained through commercial supply. The study was monitored by the MDACC Investigational New Drugs (IND) office and registered at clinicaltrials.gov (NCT02267278).

Results

Patients

Of the 25 patients enrolled on the study, five never began pracinostat and are not considered further. These five patients came off the study prior to pracinostat initiation for the following reasons: one proceeded to allogeneic hematopoietic cell transplantation (allo-HCT), one experienced disease transformation to acute myeloid leukemia (AML), two had new cancer diagnoses after study enrollment, and one was taking a prohibited medication that could not

be discontinued. Baseline characteristics of the 20 patients who received both study drugs are summarized in Table 1. The diagnosis was PMF in three quarters of the patients; no patient had post-ET MF. A driver mutation was identified in all but one patient. Just over half the patients were previously untreated. Eighty five percent had intermediate-2 or high risk disease by the IPSS.

Pracinostat dose interruption, modification and discontinuation

Pracinostat was held in 16 patients, and never restarted in six. Of the ten patients in whom pracinostat was resumed, the dose was lowered to 45 mg in nine; one patient, in whom the drug was held for back surgery, resumed pracinostat at 60 mg. Reasons for interruption/dose reduction or pracinostat in these nine patients included anemia/increased red cell transfusion requirement in three, fatigue in two, diarrhea in one, thrombocytopenia in one, anemia and thrombocytopenia in one, and anemia and nausea in one. One patient began pracinostat at a dose of 45 mg based on investigator decision because of advanced age, anemia and erythrocyte transfusion requirements. All patients eventually discontinued pracinostat, and are currently off study. Reasons for discontinuation of pracinostat were cytopenias in eight, disease progression in three, non-hematologic toxicity, unrelated medical complications, financial constraints and physician/patient perception of lack of benefit in two patients each, and allo-HCT in one (Table 2). The median time on pracinostat was 5.3 (0.4–28.4) months. The median number of cycles on study was 11.5 (5–34). The median dose of ruxolitinib was 20 mg twice daily. Ruxolitinib dose reductions to offset pracinostat-induced anemia did not occur.

Efficacy

Sixteen patients (80%) had objective responses, all CI. No patient experienced a PR or CR. Ten patients experienced CI in terms of spleen and symptoms, three spleen only, two symptoms only, and one had patient had CI-spleen as well as a partial molecular response. One patient had a baseline palpable spleen length of <5 cm and was, therefore, not evaluable for spleen response; 14 of 19 (74%) evaluable patients had CI-spleen at any time on the study. Similarly, five patients were not evaluable for symptoms response (TSS not calculated at baseline in two and TSS <12 in three); thus, the rate of CI-symptoms was 80% (12 of 15 evaluable patients). There were no anemia or cytogenetic responses. The median time to response was 1.6 (0.9–15.9) months. Fourteen patients had their earliest response prior to starting pracinostat, i.e. on ruxolitinib alone. The median duration of (earliest) response was 7.5 (3.6–25.7) months. A total of five patients had IWG-MRT responses after initiation of pracinostat, a median of 2.8 (0.9–13.1) months after starting. In two of these patients, their earliest response occurred after commencing therapy with pracinostat; in two others, spleen responses occurred after introduction of pracinostat, while symptom responses had occurred earlier, and one patient had a spleen response to ruxolitinib alone, while their symptom response occurred after therapy with pracinostat was begun. Two patients with spleen responses to ruxolitinib alone experienced resolution of palpable splenomegaly after the addition of pracinostat.

Bone marrow fibrosis grade improved in three patients, all after pracinostat initiation: from MF-3 to MF-1 in two patients (at 24.9 months and 14 months) and from MF-3 to MF-2 in

one at 6.2 months, according to the European classification.[27] The patient whose bone marrow fibrosis grade went from MF-3 to MF-1 in 14 months had achieved a grade of MF-2 at 5.5 months. Bone marrow fibrosis grade worsened in three patients, and remained unchanged in eleven. Three patients were not evaluable for change in bone marrow fibrosis grade due to missing information at baseline or follow-up. One patient had a 99.6% reduction (from 65% to 0.27%) in the variant allele frequency of *JAK2*^{V617F} at 24 months; interestingly, this patient also had an improvement in bone marrow fibrosis grade from MF-3 to MF-1 over approximately the same period. Serial assessments (twice) of *JAK2*^{V617F} allelic burden were performed in only 3 patients, however, and no meaningful changes were noted in the other two. A >50% decrease in bone marrow blasts was noted in two patients, at six and eleven months, respectively.

Survival

At the data cutoff time point (May 22nd, 2018), six patients had died. The median overall survival (OS) was 33.8 months (Figure 1). The median follow-up on surviving patients was 21.4 (12.5–39.1) months. Progressive MF was the cause of death in three patients, while two patients died of pneumonia, one with acute hypoxemic respiratory failure. *Mycobacterium avium intracellulare* was cultured from the bronchoalveolar lavage fluid from the other patient. The sixth patient was transitioned to hospice because of progressive MF and expired soon thereafter.

Safety

Adverse events (AEs) at least possibly attributable to the study drugs are listed in Table 3. Most AEs were grade 1 or 2; however, anemia was very common and was grade 3 in nine patients. Grade 4 thrombocytopenia occurred in one patient. As alluded to above, six patients discontinued pracinostat because of worsening anemia/increasing red cell transfusion requirements, one because of thrombocytopenia, and one due to both anemia and thrombocytopenia. Shingles and weight gain, recognized complications of ruxolitinib treatment, were observed in three and four patients, respectively. Two patients discontinued pracinostat because of non-hematologic toxicity: acute kidney injury (reversible upon pracinostat discontinuation) in one and an allergic reaction to pracinostat in another.

Discussion

The development of HDACi for the treatment of MPN has been difficult. While these agents are clearly active, chronic, predominantly low-grade toxicities make them difficult to administer over long periods in these relatively indolent malignancies.[16] Prolonged treatment appears necessary for disease-modifying effects to emerge, at least in MF.[28] Nevertheless, at least one HDACi, givinostat, remains in clinical development,[29] and a phase 3 registration trial is planned in patients with PV. In MF, the path of clinical development for HDACi has been checkered, with limited single-agent activity observed, both in our own experience with pracinostat[21] and that of others with a “pan”-HDACi, panobinostat.[30, 31]

In a phase 2 trial reported by DeAngelo and colleagues,[30] panobinostat (40 mg three times a week) was associated with a high discontinuation rate, and only one patient achieved an objective (IWG-MRT) response. Although correlative studies revealed inhibition of JAK/signal transducer and activator of transcription (STAT) signaling, decreased intracellular cytokine levels and *JAK2*^{V617F} allelic burden, tolerance was poor with high rates of thrombocytopenia and diarrhea. Mascarenhas *et al* reported an ORR of 36% to panobinostat in a separate, single-institution phase 2 trial employing a dose of 25 mg three times a week.[31] One patient obtained a complete molecular response, although the mean reduction in *JAK2*^{V617F} allele burden was only 6.8%. Treatment discontinuation was frequent because of physician/patient perception of therapy ineffectiveness, but six patients remained on treatment for a median of 18 months.

In our study, pracinostat was poorly tolerated, with anemia/worsening red cell transfusion requirements being a major reason for discontinuation of pracinostat. While it is tempting to speculate that this may, at least in part, be due to suppression of erythropoietin production through pracinostat-mediated down-regulation of hypoxia-inducible factor 1-alpha (HIF1-α),[32, 33] only one patient had their erythropoietin level measured on the study, prior to initiation of pracinostat, and this patient did not have a baseline erythropoietin level measured. Another patient had an erythropoietin level checked 5.5 months after coming off the study (because of anemia attributed to pracinostat), and it was higher than the baseline value for that patient. Despite the ORR (80%) and rates of spleen response (74%) and symptom improvement (80%) being high, most patients had their initial response before the introduction of pracinostat, and although additional responses, as well as deepening of initial responses, occurred in some patients after beginning therapy with pracinostat, it was difficult to quantify the added benefit of pracinostat as response rates to ruxolitinib do improve over time.[6, 7] Inclusion of a ruxolitinib-only comparator arm may help clarify the added benefit, if any, of a second agent in the upfront setting, but such designs are often impractical in small, early phase proof-of-concept trials of rational, ruxolitinib-based combination regimens. Indeed, many current trials, e.g., ref.[34], are exploring an “add-on” strategy, where a novel agent is added in patients with an insufficient response to ruxolitinib. All patients in our study eventually discontinued pracinostat, along the lines of the above experience with panobinostat. A phase 1/2 study in Europe evaluating the combination of ruxolitinib and panobinostat identified the recommended phase 2 dose for the combination and reported promising rates of ≥35% spleen volume reduction (SVR) by imaging at 24 and 48 weeks, as well as improved bone marrow fibrosis and ≥20% decrease in *JAK2*^{V617F} allele burden at 48 weeks in some patients but that trial was halted early.[35] The attainment of near-CMR in one of our patients, who remained on study for over two years, accompanied by a robust decrease in bone marrow fibrosis, is intriguing and raises the possibility of a disease-modifying effect of prolonged HDACi treatment, but such responses are also occasionally seen with ruxolitinib treatment alone.[36, 37] However, given the small number of patients in our study, that three patients had objective improvements in degree of bone marrow fibrosis at relatively early time points is somewhat striking and suggests a biological effect of pracinostat in this regard. In COMFORT-2, only 15.8% of patients randomized to ruxolitinib had improvement in bone marrow fibrosis after five years of follow-up.[7] The lack of spleen volume assessment by imaging was an obvious limitation of our investigator-

initiated study. Additionally, very few of our patients had serial assessment of driver mutation allele burden.

In general, the development of rational, ruxolitinib-based combinations for clinical use in MF has been challenging. Clinical trials of ruxolitinib in combination with inhibitors of phosphatidylinositol-3-kinase[38] and the hedgehog pathway (smoothened antagonists)[39] were stopped for lack of a significant advantage over ruxolitinib alone, at least at early time points. Other ruxolitinib combinations based on laboratory evidence of synergism, such as those with HSP90 inhibitors[15], BH3-mimetics[40] and bromodomain extra-terminal (BET) inhibitors[41] have just entered the clinic, while other concepts, e.g., combinations with inhibitors of mutant isocitrate dehydrogenase[42] and poly (ADP-ribose) polymerase (PARP) inhibitors[43] await translation. The present study does not support continued development of pracinostat for MF. Whether any of the other laboratory-based combinations being explored will succeed in the clinic remains to be seen. In contrast, encouraging early results have been reported with novel agents that counteract ruxolitinib-induced anemia, potentially enabling patients to stay on ruxolitinib for longer periods of time and optimize dosing of the only agent thus far to prolong survival in MF.[44] Bone marrow fibrosis reduction and improvement in cytopenias have also been reported with PRM-151 (recombinant pentraxin-2),[45] and data from a larger trial of this agent are eagerly awaited.

In summary, in this small, investigator-initiated trial, the addition of pracinostat to ruxolitinib resulted in only modestly increased efficacy that was difficult to attribute to pracinostat versus longer exposure to ruxolitinib. Additionally, pracinostat appeared to worsen anemia in a number of patients, and discontinuation for this and other reasons was frequent. In contrast to AML, for which pracinostat has received “breakthrough” designation from the FDA, our results do not support continued development of this agent for MF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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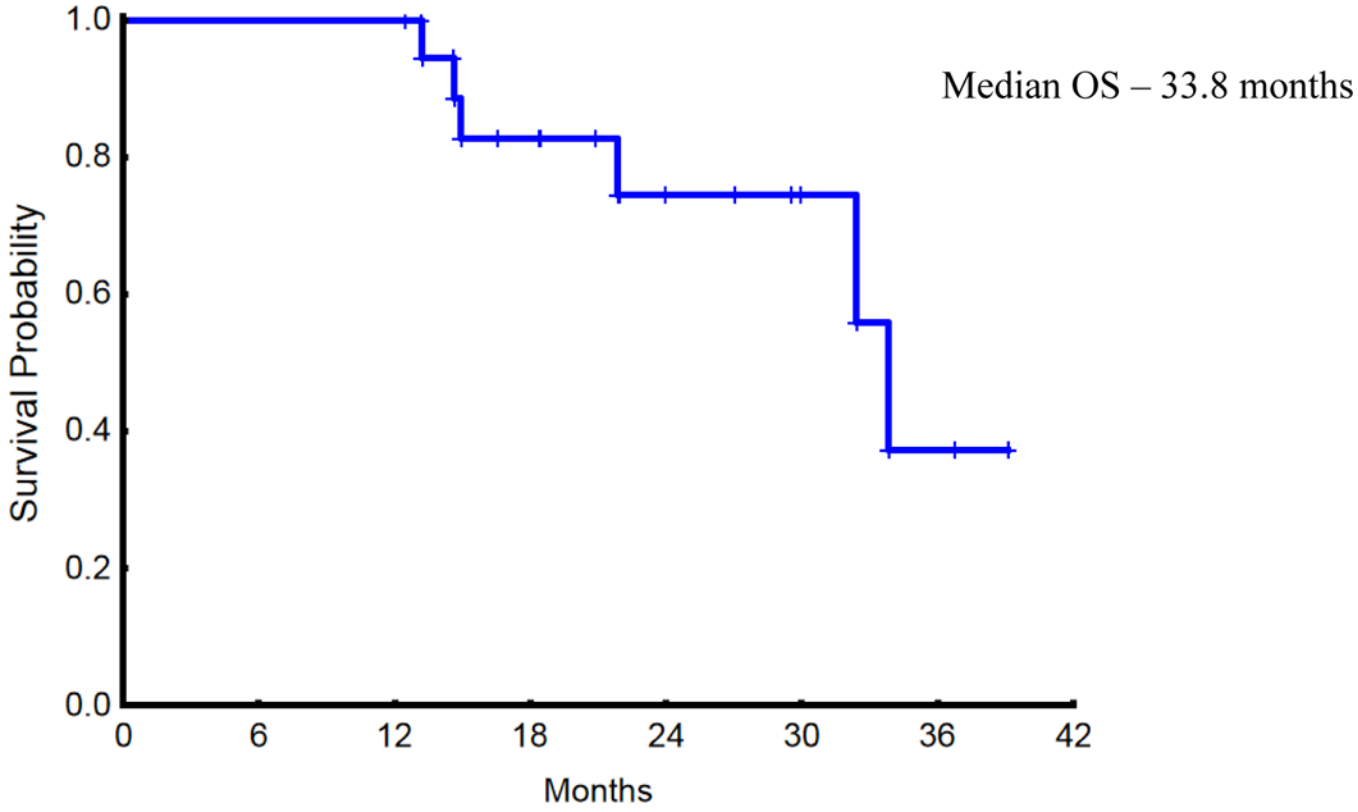

Figure 1 –.
Overall Survival of the 20 Study Patients who Received Pracinostat.

Table 1.

Baseline Characteristics of the 20 Patients who Received Pracinostat.

Variable	n (%), [range]
Median age, in years	66 [56–78]
Male sex	13 (65)
Myelofibrosis subtype	
Primary myelofibrosis	15 (75)
Post-polycythemia vera myelofibrosis	5 (25)
Post-essential thrombocythemia myelofibrosis	0
IPSS risk status	
High	11 (55)
Intermediate-2	6 (30)
Intermediate-1	3 (15)
Previously treated[¶]	9 (45)
Bone marrow fibrosis grade	
MF-1	3 (15)
MF-2	8 (40)
MF-3	8 (40)
Not available	1 (5)
Median WBC count, K/μL	10.2 [3.5–54.3]
Median platelet count, K/μL	253 [107–698]
Median hemoglobin, g/dL	10.9 [7.4–16.2]
Median palpable spleen length, cm	13 [5–20]
Driver mutation status	
JAK2 V617F	17 (85)
MPL[*]	1 (5)
CALR[‡]	1 (5)
Triple negative	1 (5)

Abbreviations: IPSS; International prognostic scoring system; WBC; White Blood Cell.

[¶]6 patients had received 1 prior therapy; 1 patient each had received 2, 3 and 5 prior therapies.

[*]17/20 patients were tested for *MPL* gene mutation.

[‡]14/20 were tested for *CALR* gene mutation.

Table 2.

Reasons for Pracinostat Discontinuation.

Patient disposition	**n (%)**
Cytopenias	
Anemia/increasing transfusion requirements	6 (30)
Thrombocytopenia	1 (5)
Anemia and thrombocytopenia	1 (5)
Disease progression	
Progressive myelofibrosis	2 (10)
Transformation to acute myeloid leukemia	1 (5)
Allogenic stem cell transplant	1 (5)
Non-hematological toxicity	
Acute kidney injury	1 (5)
Allergic reaction	1 (5)
Physician/patient perception of lack of benefit	2 (10)
Financial	2 (10)
Unrelated medical reasons	
Myocardial infarction	1 (5)
Recurrence of skin cancer requiring therapy	1 (5)

Table 3.

Adverse Events at least Possibly Related to the Study Drugs (n = 20).

Adverse Events*	Grade			
	1	2	3	4
	n (%)			
Hematological toxicity				
Anemia	2 (10)	6 (30)	9 (45)	0
Thrombocytopenia	5 (25)	2 (10)	2 (10)	1 (5)
Neutropenia	0	1 (5)	0	0
Non hematological toxicity				
Weight gain	3 (15)	1 (5)	0	0
Shingles	0	3 (15)	0	0
Diarrhea	1 (5)	0	1 (5)	0
Fatigue	0	2 (10)	0	0
Nausea	1 (5)	0	0	0
Vomiting	1 (5)	0	0	0
Flatulence	1 (5)	0	0	0
Mouth sores	1 (5)	0	0	0
Pruritus	1 (5)	0	0	0
AST elevation	1 (5)	0	0	0

*Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0)