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A Phase 2 Study of Bortezomib Combined with Either Idarubicin/ Cytarabine or Cytarabine/Etoposide in Children with Relapsed, Refractory or Secondary Acute Myeloid Leukemia: A Report from the Children's Oncology Group

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Abstract

Background—This Phase 2 study tested the tolerability and efficacy of bortezomib combined with reinduction chemotherapy for pediatric patients with relapsed, refractory or secondary acute myeloid leukemia (AML). Correlative studies measured putative AML leukemia initiating cells (AML-LIC) before and after treatment.

Procedure—Patients with <400 mg/m² prior anthracycline received bortezomib combined with idarubicin (12 mg/m² days 1–3) and low-dose cytarabine (100 mg/m² days 1–7) (Arm A). Patients with ≥400 mg/m² prior anthracycline received bortezomib with etoposide (100 mg/m² on days 1–5) and high-dose cytarabine (1 g/m² every 12 hours for 10 doses) (Arm B).

Results—Forty-six patients were treated with 58 bortezomib-containing cycles. The dose finding phase of Arm B established the recommended Phase 2 dose of bortezomib at 1.3 mg/m² on days 1, 4, and 8 with Arm B chemotherapy. Both arms were closed after failure to meet predetermined

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efficacy thresholds during the first stage of the two-stage design. The complete response (CR + CRp) rates were 29% for Arm A and 43% for Arm B. Counting additional CRi responses (CR with incomplete neutrophil recovery), the overall CR rates were 57% for Arm A and 48% for Arm B. The 2-year overall survival (OS) was $39 \pm 15\%$. Correlative studies showed that LIC depletion after the first cycle was associated with clinical response.

Conclusion—Bortezomib is tolerable when added to chemotherapy regimens for relapsed pediatric AML, but the regimens did not exceed preset minimum response criteria to allow continued accrual. This study also suggests that AML-LIC depletion has prognostic value.

Keywords

AML; AraC; pediatric oncology; relapse; Velcade

Introduction

Bortezomib (PS-341, Velcade), is a selective inhibitor of the 26S proteasome, is involved in protein degradation and is an integral part of the ubiquitin proteasome pathway [1,2]. Several studies have shown that proteasome number and activity are increased in hematologic malignancies, including AML and ALL [3–5]. In addition to its activity in multiple myeloma [6,7] and lymphoma [8], bortezomib has shown promising activity against leukemias in the pediatric preclinical testing program (PPTP) [9] and has been shown to be an effective adjuvant in two adult AML clinical trials [10,11]. Bortezomib appears to also specifically sensitize AML cells to cytarabine and anthracyclines, two agents commonly used in induction chemotherapy [12–14]. In addition, a clinical trial of bortezomib in relapsed ALL done by Messinger et al. [15,16] showed that bortezomib was effective in this difficult to treat population.

Previous studies have shown that AML originates from rare, self-renewing leukemia initiating cells (LIC) that differ from their progenitors in several respects, including their capacity for extensive growth and self-renewal [17–20]. LIC have unique stem cell gene expression signatures [21–23], dysregulated protein expression [24], and altered response to the bone marrow (BM) microenvironment [25]. Studies have shown that high AML stem cell frequency and AML-LIC engraftment in NOD/SCID mice correlates with high minimal residual disease (MRD) and poor event-free survival (EFS) [26,27]. Patients with relapsed AML often have increased LIC at diagnosis, a feature reported to be associated with poor prognosis [26].

Attar et al. [11] treated 31 adult patients with either relapsed AML ($n = 9$) or adults >60 years with newly diagnosed AML ($n = 22$) on a Phase 1 dose escalation study of bortezomib with idarubicin and cytarabine. This study reported a complete response (CR) of 61%, with an overall response rate (ORR; CR + CRp) of 71%. A second study treated 95 newly diagnosed, older adult AML patients with daunorubicin (60 mg/m^2 days 1–3), cytarabine (100 mg/m^2 , days 1–7), and bortezomib (1.3 mg/m^2 days 1, 4, 8, and 11), followed by two courses of consolidation chemotherapy with cytarabine (2 g/m^2 days 1–5) and bortezomib [11]. The CR rate in this population was 65%.

Two pediatric Phase 1 studies have established the dose of bortezomib as 1.3 mg/m in both solid tumors and leukemia [28,29]. Bortezomib was well tolerated; possible bortezomib-related grades 3 and 4 toxicities included myelosuppression, bacteremia, zoster with or without neuralgia, and peripheral sensory neuropathy [30]. Based on data from both adults and children, bortezomib was added to chemotherapy for pediatric patients with relapsed AML using: (i) idarubicin and cytarabine (Arm A); or (ii) high-dose cytarabine (1 g/m²) and etoposide (Arm B).

Methods

Study Population

The Children's Oncology Group (COG) study AAML07P1 was open from April 2008 through December 2011. The eligibility criteria for the study included refractory, relapsed or treatment-related AML. The dose finding phase was limited to relapsed patients without favorable cytogenetics (t(8;21) or inv16), while the efficacy phases were limited to patients with refractory, treatment-related, or first relapse AML. Other eligibility criteria included: age >12 months and ≤30 years; ≤5% marrow myeloblasts; no prior reinduction chemotherapy (efficacy phase), <5/μL myeloblasts in CSF (CNS1 or CNS2), performance level (Lansky/Karnofsky) ≥50; no prior cytotoxicity therapy in 2 weeks; no prior steroids in 7 days; no prior radiation for 2 weeks (small port), 6 weeks, or 8 weeks (pelvis or craniospinal); at least 2 months from stem cell transplant with no evidence of graft versus host disease; and adequate organ function including adequate renal, cardiac, liver, and pulmonary function (pulse oximetry >94% with normal respiratory rate, normal pulmonary function tests). Patients with a seizure disorder could be enrolled if seizures were well controlled on a non-enzyme inducing anticonvulsant and if CNS toxicity had resolved to grade 2. Exclusion criteria included uncontrolled infection, known allergy to idarubicin, cytarabine, etoposide, boron, mannitol or bortezomib; prior radiotherapy that included >25% of lung volume or prior total body irradiation; growth factors within 4 days of study entry, concomitant treatment with p450 enzyme-inducing anticonvulsants, or other investigational agents; pregnancy or breast feeding. Prior treatment-related toxicities had to have resolved to grade 2. Informed consent was obtained from the patient or their parent(s) and assent, as appropriate, were obtained in accordance with the U.S. National Cancer Institute, the Children's Oncology Group, and individual institutional review board policies prior to study entry.

Definitions of Evaluability and Response

Evaluability—Patients were considered evaluable for response if they received at least one dose of bortezomib and were either a treatment failure or had a disease evaluation after cycle 1. Those patients who attained a complete response (CR) or CRp (CR with partial recovery of platelet count) were considered responders. Those who achieved all other responses (including CRi, PR, TF, or death during cycle 1) were considered treatment non-responders. Patients were considered evaluable for toxicity if they had received at least one dose of bortezomib and either had a toxicity during the first cycle or completed the first cycle without toxicity.

Response—Response criteria conformed to the revised AML International Working Group Criteria [31,32]. CR required attainment of an M1 bone marrow (<5% blasts) with no evidence of circulating blasts or extramedullary disease, and with recovery of peripheral blood counts (ANC $\geq 1,000/\mu\text{L}$ and platelet count $\geq 100,000/\mu\text{L}$). CRp was defined as CR without platelet transfusion independence (defined as no platelet transfusions $\times 1$ week). CR with incomplete blood count recovery (CRi) required an ANC $< 1,000/\mu\text{L}$ with or without platelet recovery. Partial response (PR) required at least 50% decrease in the percentage of blasts to 5–25% myeloblasts in the bone marrow aspirate (M2 marrow) with adequate marrow cellularity ($> 15\%$). Treatment failure was defined as any M2 or M3 marrow that did not qualify for PR.

Trial Design and Therapy

Patients were nonrandomly assigned to either Arm A or Arm B based on prior anthracycline exposure. Those with a prior cumulative anthracycline dose of $\leq 400 \text{ mg/m}^2$ were eligible for Arm A, which consisted of idarubicin (12 mg/m^2 on days 1–3), cytarabine (100 mg/m^2 on days 1–7 by continuous IV infusion), and bortezomib (1.3 mg/m^2 on days 1, 4, and 8). Patients with $>400 \text{ mg/m}^2$ prior anthracycline exposure were eligible for Arm B, consisting of high-dose cytarabine (1 g/m^2 q12 hours on days 1–5), etoposide (150 mg/m^2 on days 1–5) and bortezomib using the same schedule. In the dose finding phase of Arm B, bortezomib was administered at two dose levels (1 and 1.3 mg/m^2) on days 1, 4, and 8. In the efficacy phase, bortezomib was administered at a dose of 1.3 mg/m^2 .

For the efficacy phase of both arms, the study employed a two-stage design that considered both response and toxicity [33]. The two-stage design was constructed to test the null hypothesis that the ORR was $\leq 40\%$ versus the alternative hypothesis that the ORR was $\geq 60\%$, based on a previous study of relapsed AML (CCG-2951) [34], and required CR+CRp of 6 or more of the first 14 patients for Arm A and 11 or more of the first 24 patients in Arm B. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria v4.0. Bone marrow aspiration for assessment for morphologic response was required between days 28 and 33 of protocol therapy and, if inevaluable, bone marrow aspirations were repeated weekly through day 49. Subsequent treatment after the first cycle of protocol therapy was left to the discretion of the treating physician. A second cycle of protocol therapy was allowed for patients with a response of better than SD. Supportive care guidelines included pneumocystis prophylaxis (trimethoprim/sulfamethoxazole, dapsone, atovaquone, or pentamidine); antifungal prophylaxes (caspofungin or voriconazole) were required from day 10 of cycle 1. Azole antifungal therapy was discouraged from days -2 to $+10$ due to concern about interactions with the p450 system and bortezomib metabolism. No prophylactic antibiotics were required.

Statistical Methods

The primary endpoint of the dose finding phase was to determine the maximum tolerated dose (MTD) of bortezomib (up to a dose of 1.3 mg/m^2) when given with high-dose cytarabine and etoposide (Arm B). In this phase, a minimum of three patients were entered at each dose level and the dose level was expanded to up to six patients when one patient experienced dose-limiting toxicity during the first cycle of therapy. The primary endpoints

of the efficacy phase were: (i) toxicity and tolerability of bortezomib in combination with standard chemotherapy in either regimen A or B; and (ii) overall response (CR + CRp) rate after one cycle of therapy. The secondary endpoints were to determine the effect of the administration of bortezomib with chemotherapy on NF- κ B activity in circulating myeloblasts, and the feasibility of assessing the effects of bortezomib-containing chemotherapy on AML-LIC. There were no statistically significant differences in patient characteristics (gender, race, ethnicity, age, or response to therapy) between those patients with samples submitted for LIC and NF- κ B activity analysis and those with no available samples (exact test).

Overall survival (OS) was defined as time from study entry to death. OS was also defined as time from end of cycle 1 to death for patients who were alive at the end of cycle 1 with an evaluable response. Patients were censored for OS analyses at the date of last contact. Kaplan–Meier method was used to estimate OS, and comparisons of OS were made using the log-rank test. The significance of observed difference in proportions was tested using the Chi-squared test and Fisher's exact test when data were sparse. The Kruskal–Wallis test was used to determine the significance between differences in medians of groups. *P* values < 0.05 were considered significant.

Correlative studies: See supplemental methods online.

Results

Patients

COG AAML07P1 enrolled 46 eligible and evaluable patients (14 on Arm A and 32 on Arm B). Three patients enrolled at the final dose level of the dose finding phase for Arm B also met the eligibility criteria for the Arm B efficacy phase, and they were included in the analysis of the Arm B efficacy phase, for a total of 23 eligible patients in the efficacy phase. Table I provides a summary of patient characteristics at study entry for all eligible and evaluable patients. Four patients enrolled on the study were declared ineligible due to: (i) <5% blasts in pre-treatment bone marrow (Arm A), (ii) inability to obtain CSF prior to initiation of therapy (Arm A), (iii) history of allergy to etoposide (Arm B); and (iv) an inability to meet minimum lung function requirements (Arm B). Two patients on Arm A were deemed inevaluable due to incorrect study arm assignment based on prior anthracycline exposure.

Phase 1 Dose Finding Phase

In the first cohort of three patients at a bortezomib dose of 1.0 mg/m², one patient experienced a dose-limiting toxicity (infection with multi-organ system failure), requiring expansion of the cohort with another three patients. No DLT's were observed in this cohort. At the next and predetermined highest dose level of 1.3 mg/m² there were no DLTs among the six patients entered. Therefore, the dose of bortezomib for the Arm B efficacy phase was determined to be 1.3 mg/m².

Toxicity

Table II is a summary of all reported major (grade 3 or higher) non-hematologic toxicities attributable to bortezomib for all cycles. Most of the toxicities were related to infection. There was a higher than expected incidence of hypokalemia, with 19% of cycles in Arm A and 17% of cycles in Arm B having grade 3 or higher hypokalemia. Serious toxicities in Arm A included one case each of grade 4 hypotension and grade 3 abdominal pain, ileus, vascular access complication, and pneumonitis; Arm B serious toxicities included 1 case each of grade 4 bilirubin, grade 4 pulmonary edema, grade 3 diarrhea, esophageal pain, chest pain, increased ALT, increased creatinine, hypercalcemia, hyperglycemia, hypoalbuminemia, hypomagnesemia, back and bone pain, ARDS, palmar-erythrodesesthesia, maculopapular rash, and allergic reaction. There were no cases of grade 3 or 4 peripheral neuropathy. This toxicity rate is comparable with other pediatric trials in relapsed leukemia [35–37].

There were four deaths reported within 30 days of protocol therapy. Two infectious deaths occurred in the Arm B dose finding phase: one patient with grade 5 sepsis with multi-organ system failure, and one patient with grade 5 fungal sepsis during stem cell transplant following protocol therapy. Two deaths occurred in Arm A: one from grade 5 bacterial sepsis with cardiac decompensation, and one from progressive disease.

Response

The response by the end of cycle 1 of patients enrolled in the efficacy phases is shown in Table III. Arm A responses were: 3 CR, 1 CRp, 4 CRi, 2 PR, and 4 treatment failure (TF). Arm B responses were: 8 CR, 2 CRp, 1 CRi, and 11 TF. Both arms did not meet the criteria for progression to stage 2, although both would have met the criteria had CRi been included as a response. The 29% CR + CRp response rate (95% CI: 8–58%) increased to 57% if including CR, CRp, and CRi. Similarly, the 43% CR + CRp rate (95% CI: 23–66%) in Arm B increased to 48% if including CR, CRp and CRi.

The OS of patients enrolled in the efficacy phase of both arms is shown in Figure 1A. There was no difference in OS between study arms, and the combined 2-year overall survival (OS) of both groups ($39 \pm 15\%$) is comparable to other studies of relapsed AML [38]. The difference in OS between subjects with response of CR + CRp versus CRi versus PR + TF is shown in Figure 1B. In the efficacy phase stopping rules, CRi was not considered as response, yet the OS of this group is comparable to patients who achieved CR or CRp. When all CR (CR, CRp, and CRi) are considered as a treatment success (TS), the difference in OS between TS and TF is statistically significant ($P = 0.011$). The comparison suggests that CRi response was a clinically meaningful response that results in outcomes similar to CR and CRp.

Correlative Studies

This Phase 2 study included the feasibility objective of assessing leukemia-initiating cells (LICs) during the first cycle of bortezomib-containing chemotherapy, the ability to quantitate NF- κ B activity in myeloid blast cells. Of the 46 eligible and evaluable patients

enrolled on the trial, 17 had pre-treatment bone marrow available for LIC analysis (37%) and 30 day-1 peripheral blood samples available for NF- κ B analysis (65%).

LIC assessment: Of the 17 patients with evaluable pre-treatment bone marrow, 15 had detectable LIC. Pre-treatment LICs ranged from 0.001% to 5.3% (Fig. 2). The median pre-treatment LIC in the patients attaining a CR was 2%; the median pre-treatment LIC in those attaining less than a CR was 0.12% ($n = 15$, $P = 0.34$, Kruskal–Wallis test). Post-treatment LIC were quantifiable in 10 patients. All five patients that achieved a CR had no ($n = 4$) or minimal ($n = 1$, 0.001%) LIC following one cycle of bortezomib-containing chemotherapy (Table SI). In contrast, four of five non-CR patients had detectable LIC following treatment. Despite small numbers ($n = 5$ per group), the difference in percentage of post-induction LIC was significantly different between those attaining CR and those attaining less than CR ($P = 0.045$, Wilcoxon rank sum test). In the six patients with evaluable LIC sample pairs (pre-treatment and end of cycle 1), LIC were depleted in two patients attaining a CR, and stable or increased in three of the four patients with a response less than CR. The remaining patient with treatment failure, however, had complete LIC depletion, implying that LIC depletion alone is not sufficient for CR attainment.

NF- κ B binding activity: Specimens to evaluate NF- κ B levels were obtained from 36 patients. Unlike samples from patients with lymphoid malignancies, non-malignant PBMC, and non-malignant bone marrow [29], 25 of 36 patient myeloblast samples had undetectable NF- κ B binding activity. In the 11 patients with evaluable NF- κ B activity in peripheral myeloblasts, there was a statistically significant increase in NF- κ B activity 2 hours after cytotoxic chemotherapy (either idarubicin/cytarabine or cytarabine/etoposide), which decreased to baseline at 24 hours (Fig. 3). However, there was no discernible difference between pre- (0 hour) and post- (24 hours) treatment NF- κ B activity.

Discussion

This study demonstrated the feasibility of adding bortezomib to chemotherapy for childhood AML. While the outcomes were not significantly different than in other studies of relapsed pediatric AML, it is the first time that LIC have been assessed during pediatric AML therapy, and the findings suggest that bortezomib-containing chemotherapy can deplete AML-LIC.

Since there had been rare reports of severe pulmonary toxicity in patients receiving bortezomib either as a single agent [39,40] or in combination with high-dose cytarabine, the arm of the study in which bortezomib was combined with high-dose cytarabine (Arm B) was initially opened in a dose finding phase to confirm regimen safety. The dose finding phase of the study established the standard dose of bortezomib at 1.3 mg/m^2 as a safe dose when given in combination with high-dose cytarabine, and the efficacy phases of both arms demonstrated that bortezomib was tolerable when given at this dose in combination with the two different AML chemotherapy regimens

The two-stage design in this clinical trial incorporated an interim analysis for both toxicity and efficacy and set thresholds, based on historical data, for further study enrollment [41].

These criteria excluded CRi from the response definition. The relatively large number of CRi responses in Arm A potentially skewed the response results in this arm of the study. In this study, the survival of patients with a CRi matched those attaining CR and CRp. This suggests that CRi was a similar response to CR and CRp. The number of CRi responses and the exclusion of CRi responses from the definition of efficacy shortened the study and may have obscured the determination of the efficacy of bortezomib in pediatric AML. An increase in bone marrow recovery times due to prior marrow damage is not unexpected in patients that have previously received highly myelosuppressive chemotherapy. This makes the analysis of new agents when combined with standard relapsed AML challenging. Response definitions were set at CR and CRp to allow more meaningful comparisons with the historical controls used to establish null hypothesis response rate. Moving forward CRi will be included in definition of response in future studies.

The integrated laboratory studies represent important feasibility tests to define the role of NF- κ B and LIC in treatment response to bortezomib-containing regimens in pediatric AML. Both assays were intended to assess the potential mechanisms of action of bortezomib. As a proteasome inhibitor (PI), bortezomib prevented degradation of I- κ B, an NF- κ B inhibitor. I- κ B binds and sequesters NF- κ B in the cytoplasm, preventing NF- κ B nuclear translocation and transcriptional activation of NF- κ B substrates. Many of these substrates are anti-apoptotic and thought to induce chemoresistance. Since LIC have been shown to have elevated NF- κ B activity [42], we hypothesized that PI therapy would specifically targeted LIC through NF- κ B inhibition. However, LIC analysis was limited due to the lack of availability of diagnostic bone marrow samples for LIC testing (17/46). Many diagnostic bone marrows on relapsed patients were performed at sites other than the treating COG institution, and these bone marrow samples were unavailable for analysis, decreasing the power of our observations.

Assessment of NF- κ B activity was challenging in the setting of a multi-institution study. Of the 36 samples tested, 30 had sufficient peripheral blood for analysis (four-bone marrow only, two-pre-treatment sample only). In contrast to other studies involving lymphoid malignancies [29,43] we found that 20/30 (67%) of patients with relapsed AML had undetectable myeloblast NF- κ B activity. To determine if this high number of undetectable NF- κ B cases was due to AML or the shipping process, we also examined NF- κ B activity in relapsed AML samples from patients treated locally. In locally processed pediatric relapsed AML samples, only 3/10 had undetectable NF- κ B activity. This suggests that at least part of our inability to detect NF- κ B activity in COG AML samples was due to a decrease in AML NF- κ B activity during sample shipment. Based on publications about the contextual role of NF- κ B in proteasome inhibition [42,44–47], other COG studies are now examining NF- κ B in the context of other signal transduction and cell stress pathways induced by inhibition of proteasome-mediated protein degradation.

The second biologic objective of this study was to quantify AML-LIC before and after bortezomib-containing chemotherapy. Although there is considerable inter-patient heterogeneity in AML-LIC [21,48]; LIC can often be identified by individual aberrant immunophenotype markers that distinguish the LIC from normal hematopoietic stem cells (HSC) [49]. Previous work has shown that AML-LIC have increased NF- κ B expression,

which may protect cells from undergoing apoptosis following chemotherapy [17]. This makes LIC a target for proteasome inhibitor therapy, since bortezomib blocks NF- κ B activation [14,18,50]. The results of this study suggest that AML-LIC depletion correlates with response to therapy.

In summary, this study demonstrates that bortezomib can be safely combined with combination chemotherapy (either idarubicin + low-dose cytarabine or high-dose cytarabine + etoposide) in pediatric patients with relapsed AML. It also suggests that bortezomib-containing chemotherapy can deplete AML-LIC. The role of bortezomib in pediatric AML therapy and in achieving AML-LIC depletion will be further tested in a randomized, Phase 3 study currently being conducted by the COG.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. (A) Overall survival (OS) from study entry of all eligible patients enrolled in efficacy phases of Arms A and B. (B) Overall survival (OS) from the end of cycle 1 by definition of clinical response at the end of cycle 1.

Fig. 2.

(A) Percentage of pre-treatment LIC determined from enrolled patients with evaluable flow analysis data. LIC are determined as discussed in Methods and Materials. Open bars: patients with a CR; grey bars; PR, black bars, treatment failure.

Fig. 3.

Relative NF-κB activity in eleven patients prior to treatment (0 hour), 2 hours after chemotherapy (either idarubicin/cytarabine, n = 4 or cytarabine/etoposide, n = 7), 1 hour after bortezomib (3 hours) and 24 hours after the start of chemotherapy. Statistically significant differences are bracketed.

TABLE I
Characteristics of Eligible Patients in Efficacy Phase of Arms A and B

	Arm A: cytarabine, idarubicin, bortezomib (n = 14)	Arm B: cytarabine, etoposide, bortezomib (n= 23)
Gender		
Male	7	9
Female	7	14
Race		
White	9	18
African American	2	3
Asian	1	1
Unknown	2	1
Ethnicity		
Hispanic or Latino	2	3
Not Hispanic or Latino	10	18
Unknown	2	2
Is patient refractory to induction therapy (with no more than one attempt at remission induction)?	2	2
Treatment-related AML	5	5
Age at diagnosis (years) — median (range)	10 (1.2 – 19.6)	6.1 (0.2 – 16.2)

TABLE II
Grades 3 and 4 Adverse Events (Cycles 1 and 2) Attributable to Bortezomib

Adverse events	Arm A: idarubicin, cytarabine, bortezomib (n = 16 cycles)		Arm B: cytarabine, etoposide, bortezomib (n=42 cycles)	
	Total (%)	Grade 3	Grade 4	Total (%)
Infections ^a	6 (37)	5	1	20 (48)
Febrile neutropenia	4 (25)	4	—	8 (21)
Hypokalemia	3 (19)	3	—	7 (17)
Dyspnea/hypoxia	1 (6)	1	—	4 (10)
Anorexia	1 (6)	1	—	4 (10)
Nausea	—	—	—	4 (10)
Mucositis	1 (6)	1	—	3 (7)
Fever	—	—	—	3 (7)
GGT	—	—	—	3 (7)
Vomiting	—	—	—	3 (7)
Enterocolitis	—	—	—	2 (5)
Organ failure	1 (6)	—	—	1 (2)

^aInfections included 2 cases of sepsis (grade 4), 3 catheter-related infections (2 grade 3, 1 grade 4), 1 lung infections (2 cycles, grade 3), 1 upper respiratory (grade 3), 1 soft tissue infection (grade 3), 9 other (8 grade 3, 1 grade 4).

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