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Clinical use and toxicities of bortezomib in pediatric patients: a systematic review

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Background: Proteasome inhibitors (PIs) are FDA-approved to treat adult malignancies. The PI, Bortezomib (BTZ), has been used off-label in pediatric patients but its safety profile in these patients has yet to be systematically assessed. We sought to review the pediatric safety profile of BTZ based on published clinical articles which we compared to publicly available adult safety data from the BTZ drug insert.

Methods: PubMed and the Cochrane Database were searched up through September 2024. We included published clinical studies that reported adverse events (AEs) which included clinical trials, clinical studies (>10 patients), and clinical series/case reports (≤10 patients). Extracted pediatric safety data was compared to reported adult safety profile from the BTZ drug insert.

Results: There was heterogeneity in reporting of different AEs and not all categories were comparable to published adult AEs. Any studies were small case series or reports which did not allow for more quantitative analysis. Nevertheless, we found that pediatric patients treated with BTZ reported lower incidence of peripheral neuropathy and gastrointestinal toxicity compared to adults. Rates of bone marrow suppression and infection in pediatrics were comparable to or higher than those observed in adults. These incidences were comparable or lower when pediatric patients with leukemia were excluded.

Discussion: BTZ has an acceptable safety profile for use in pediatric patients. Antibacterial and antifungal prophylaxis should be considered given the high rate of infections.

KEYWORDS

bortezomib, adverse events, pediatric safety, systematic review, proteasome inhibitors

Introduction

Normal cellular homeostasis requires a balance of protein synthesis and degradation and is vital for cellular function and survival (Teicher and Tomaszewski, 2015; Cromm and Crews, 2017). Proteostasis defects causing abnormal intracellular accumulation of misfolded or damaged proteins can cause cell death (Cvek and Dvorak, 2008; Teicher and Tomaszewski, 2015; Cao et al., 2021). One mechanism for protein degradation in the cell is the proteasome degradation (PD) pathway (Ciechanover, 2005; Cvek and Dvorak, 2008; Teicher and Tomaszewski, 2015; Cao et al., 2021), which is mediated by the 26S

proteasome, consisting of a 20S core flanked by two 19S regulatory subunits (Teicher and Tomaszewski, 2015; Cromm and Crews, 2017).

Studies have shown that cancer cells are more reliant on the PD pathway to maintain homeostasis and thus more sensitive to the effects of proteasome inhibition (Delic et al., 1998; Adams, 2004; Nawrocki et al., 2005; Crawford et al., 2009; Crawford et al., 2011). Proteasome inhibitors (PIs) comprise a class of drugs that specifically target the 20S subunit of the proteasome (Teicher and Tomaszewski, 2015; Wang et al., 2021) and preferentially target cancer cells with proteostasis defects, leading to exacerbated cytoplasmic protein accumulation and cell death (Delic et al., 1998; Nawrocki et al., 2005; Teicher and Tomaszewski, 2015). Five PIs are currently in clinical use: bortezomib (BTZ), carfilzomib, marizomib, oprozomib, and ixazomib (Richardson et al., 2003b; Chauhan et al., 2005; Piva et al., 2008; Chauhan et al., 2010; Potts et al., 2011; Muz et al., 2016; Perel et al., 2016). One PI, delanzomib, is currently in clinical trials (Vogl et al., 2017).

BTZ is a first-generation PI that binds the 20S proteasome and approved in 2003 to treat refractory multiple myeloma (MM) in adults and is currently FDA approved for adult use in *de novo* and relapsed/refractory MM and relapsed/refractory mantle cell lymphoma (Raedler, 2015). While not FDA-approved for pediatric patients, BTZ has been prescribed off-label in the pediatric setting for both malignant and non-malignant indications. This systematic review serves to systematically review the safety profile of BTZ in pediatric patients from the published literature and compared to adults. The goal is to identify strategies for the safe and effective use of PIs in pediatric patients.

Patients and methods

Search strategy

A search of PubMed and the Cochrane Database of Systematic Reviews was performed in September of 2024. Search terms were separated by Boolean operators as follows: (“bortezomib”) AND (“pediatric” OR “children”). Article types were “adaptive clinical trials”, “case reports”, “clinical studies”, “clinical trials phase 1-4”, “controlled clinical trials”, “randomized controlled trials”, and “multi-center studies”. References of selected articles were searched for additional studies. In July 2025, clinical trial registries were searched on clinicaltrials.gov using the terms “bortezomib” and “pediatric”; “bortezomib” and “children”. Those registries with results posted were reviewed for inclusion or exclusion into our analysis. Findings were compared to the drug insert provided by Takeda for adult adverse events (AEs) where available (Takeda Pharmaceuticals, 2022).

Inclusion/exclusion criteria

Studies included for analysis are those that reported on pediatric patients ≤ 18 years of age treated with BTZ for all indication, as a single agent or in combination with other therapeutics. Patients ≤ 8 years of age were further stratified and defined as

young pediatric patients for analysis. Studies were excluded if they met any of the following criteria: (1) review articles, (2) preclinical studies, (3) clinical studies that included adult patients where pediatric data could not be separated, (4) trial design only, (5) patient reported outcomes, (6) did not use BTZ, and (7) not available in English.

Article selection and data extraction

Full-text articles from the initial search were reviewed independently by two authors (Z.C.L., A.C.). Data extraction was performed independently by each author and compared for accuracy prior to inclusion. Data collected included study type, date of publication, number of enrolled patients, number of patients assessed for AEs, treatment indication, co-treatment, grade and incidence of complications, dose-limiting toxicities, and deaths attributable to BTZ.

Toxicity classification

The CTCAE system was used for toxicity classification. Identified AEs were classified by organ systems and included the neurological, bone marrow, infectious, respiratory, cardiac, and gastrointestinal systems. Toxicities are reported here as individual CTCAE terms or grouped by broader organ system category based on reporting of source documents. Toxicities from the same CTCAE group were tabulated as single event when it was clear that the toxicities occurred in a single patient. Dose limiting toxicity (DLT) was defined as AEs that required dose reduction, temporary or permanent cessation of BTZ. Treatment-related mortality was defined as death within 30 days of last BTZ dose that was possibly attributed to BTZ.

Synthesis

Data was collected and analyzed using Microsoft Excel (Version 16.0). Studies that did not report on certain categories of AEs were excluded from the corresponding tabulations of patients who experienced these complications. Finally, pediatric AEs incidences were compared to those reported for adults in the commercial packaging insert for BTZ.

Results

Study selection

Search criteria across PubMed and Cochrane databases identified 183 articles of which 23 were duplicates. Screening the abstract resulted in the exclusion of 22 that were trial registrations, 31 conference proceedings, and 2 articles not available in English (Figure 1). 105 full text articles were assessed for eligibility. An additional 25 were excluded because they combined both adult and pediatric patient data from which pediatric data could not be extracted, 8 that did not use BTZ, 8 containing only laboratory

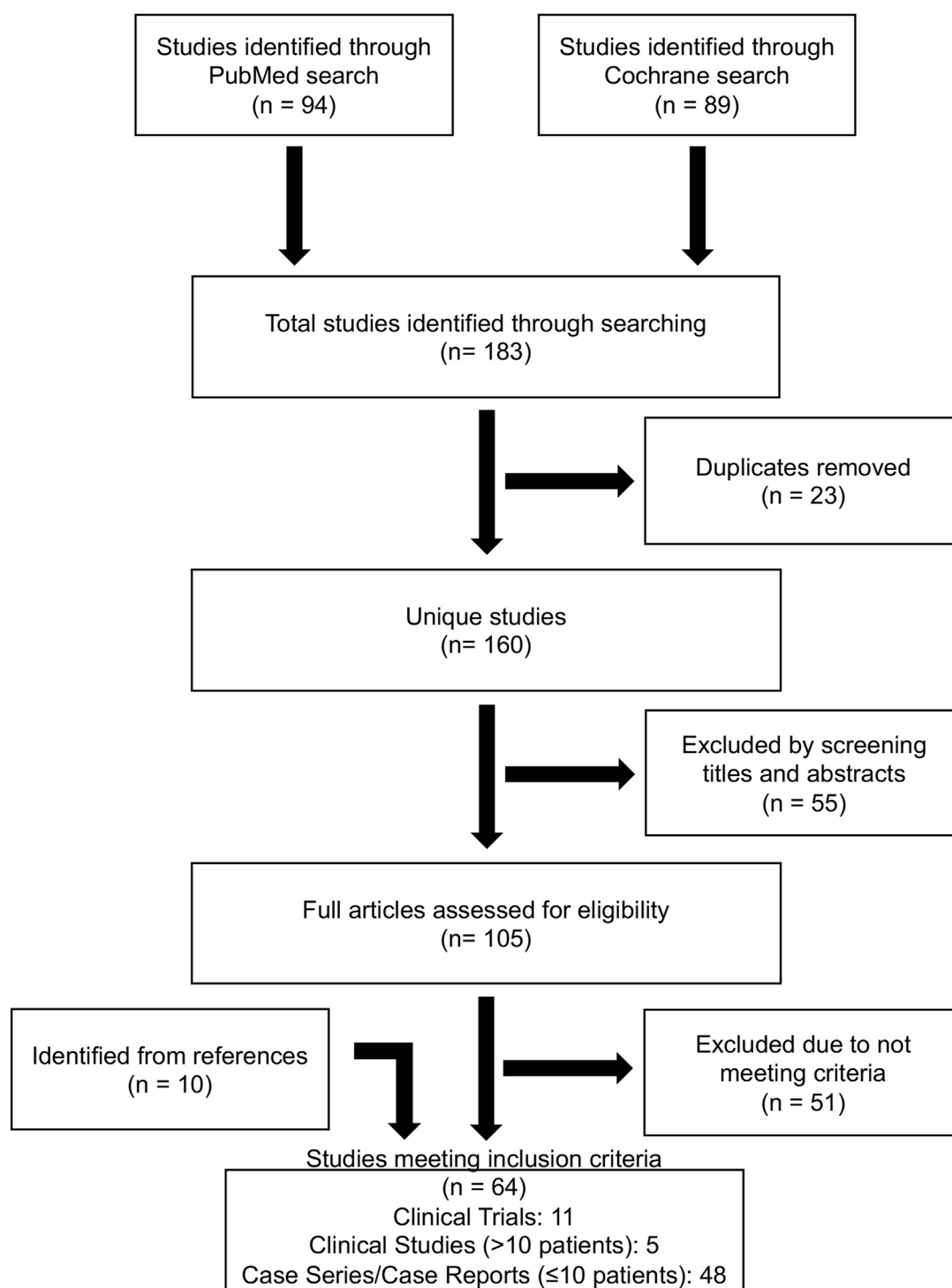


FIGURE 1
Database search strategy. PRISMA flowchart of database search, inclusion and exclusion criteria to result in eligible publications used for systematic review.

data, 9 with no discussion of adverse events, and 1 that addressed trial design theories with no reported patient interventions ($n = 54$). An additional 10 studies were found within references of identified articles. Articles were downloaded and reviewed in their entirety for data extraction and analysis. In total, 64 articles met inclusion criteria (Figure 1).

Search criteria across registered clinical trials matching “bortezomib” and “pediatric” returned 26 trials and “bortezomib” and “children” returned 10 trials. After removing duplicates 10 unique trials had posted results. Of trials with results, 3 trials were published and already included in our analysis (Figure 1), 6 trials encompassed both pediatric and adult patients and pediatric

TABLE 1 Summary of toxicities of all grades in pediatric patients treated with bortezomib.

Indication	Evaluable patients	# of adverse events	% of patients experiencing complication, all grades
Peripheral Neuropathy			
ALL	169	24	14.20%
AML	291	22	7.56%
Solid tumors	54	6	11.11%
Transplant	68	1	1.47%
Autoimmune cytopenias	20	0	0.00%
Anti-NMDA encephalitis	4	0	0.00%
Other	13	0	0.00%
Total	619	53	8.56%
ALL/AML only	460	46	10.00%
Total excluding ALL/AML	159	7	4.40%
Other Neurological			
ALL	128	5	3.91%
AML	287	0	0.00%
Solid tumors	36	1	2.78%
Transplant	68	3	4.41%
Autoimmune cytopenias	20	0	0.00%
Anti-NMDA encephalitis	4	0	0.00%
Other	13	0	0.00%
Total	556	9	1.62%
ALL/AML only	415	5	1.20%
Total excluding ALL/AML	141	4	2.84%
Anemia			
ALL	70	43	61.43%
AML	0	0	
Solid tumors	52	31	59.62%
Transplant	66	6	9.09%
Autoimmune cytopenias	20	0	0.00%
Anti-NMDA encephalitis	4	0	0.00%
Other	13	0	0.00%
Total	225	80	35.56%
ALL only	70	43	61.43%
Total excluding ALL	155	37	23.87%
Neutropenia			
ALL	117	90	76.92%
AML	0	0	
Solid tumors	52	33	63.46%
Transplant	68	4	5.88%

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TABLE 1 (Continued) Summary of toxicities of all grades in pediatric patients treated with bortezomib.

Indication	Evaluable patients	# of adverse events	% of patients experiencing complication, all grades
Autoimmune cytopenias	20	0	0.00%
Anti-NMDA encephalitis	4	1	25.00%
Other	13	0	0.00%
Total	274	128	46.72%
ALL only	117	90	76.92%
Total excluding ALL	157	38	24.20%
Febrile Neutropenia			
ALL	97	31	31.96%
AML	4	4	100.00%
Solid tumors	22	1	4.55%
Transplant	68	1	1.47%
Autoimmune cytopenias	20	1	5.00%
Anti-NMDA encephalitis	4	0	0.00%
Other	13	0	0.00%
Total	228	38	16.67%
ALL/AML only	101	35	34.65%
Total excluding ALL/AML	127	3	2.36%
Thrombocytopenia			
ALL	122	95	77.87%
AML	0	0	
Solid tumors	52	32	61.54%
Transplant	68	9	13.24%
Autoimmune cytopenias	20	3	15.00%
Anti-NMDA encephalitis	4	0	0.00%
Other	13	0	0.00%
Total	279	139	49.82%
ALL only	122	95	77.87%
Total excluding ALL	157	44	28.03%
Leukopenia			
ALL	70	56	80.00%
AML	0	0	
Solid tumors	52	26	50.00%
Transplant	35	0	0.00%
Autoimmune cytopenias	20	1	5.00%
Anti-NMDA encephalitis	4	0	0.00%
Other	13	0	0.00%
Total	194	83	42.78%
ALL only	70	56	80.00%

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TABLE 1 (Continued) Summary of toxicities of all grades in pediatric patients treated with bortezomib.

Indication	Evaluable patients	# of adverse events	% of patients experiencing complication, all grades
Total excluding ALL	124	27	21.77%
Lymphopenia			
ALL	41	24	58.54%
AML	0	0	
Solid tumors	21	11	52.38%
Transplant	35	3	8.57%
Autoimmune cytopenias	20	0	0.00%
Anti-NMDA encephalitis	4	0	0.00%
Other	13	0	0.00%
Total	134	38	28.36%
ALL only	41	24	58.54%
Total excluding ALL	93	14	15.05%
Infection			
ALL	169	54	31.95%
AML	291	203	69.76%
Solid tumors	54	0	0.00%
Transplant	68	6	8.82%
Autoimmune cytopenias	20	1	5.00%
Anti-NMDA encephalitis	4	0	0.00%
Other	13	1	7.69%
Total	619	265	42.81%
ALL/AML only	460	257	55.87%
Total excluding ALL/AML	159	8	5.03%
Respiratory toxicities, excluding those attributable to infection			
ALL	121	4	3.31%
AML	287	47	16.38%
Solid tumors	21	1	4.76%
Transplant	33	1	3.03%
Autoimmune cytopenias	20	0	0.00%
Anti-NMDA encephalitis	4	0	0.00%
Other	13	0	0.00%
Total	499	53	10.62%
ALL/AML only	408	51	12.50%
Total excluding ALL/AML	91	2	2.20%
GI			
ALL	156	13	8.33%
AML	4	0	0.00%
Solid tumors	54	33	61.11%

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TABLE 1 (Continued) Summary of toxicities of all grades in pediatric patients treated with bortezomib.

Indication	Evaluable patients	# of adverse events	% of patients experiencing complication, all grades
Transplant	68	9	13.24%
Autoimmune cytopenias	20	3	15.00%
Anti-NMDA encephalitis	4	0	0.00%
Other	13	0	0.00%
Total	319	58	18.18%
ALL/AML only	160	13	8.13%
Total excluding ALL/AML	159	45	28.30%
Cardiac			
ALL	21	2	9.52%
AML	287	17	5.92%
Solid tumors	19	1	5.26%
Transplant	35	0	0.00%
Autoimmune cytopenias	20	0	0.00%
Anti-NMDA encephalitis	4	0	0.00%
Other	13	0	0.00%
Total	399	22	5.51%
ALL/AML only	308	21	6.82%
Total excluding ALL/AML	91	1	1.10%
Dose-limiting toxicities			
ALL	169	9	5.33%
AML	291	65	22.34%
Solid tumors	54	7	12.96%
Transplant	68	2	2.94%
Autoimmune cytopenias	20	2	10.00%
Anti-NMDA encephalitis	4	0	0.00%
Other	13	0	0.00%
Total	619	85	13.73%
ALL/AML only	460	74	16.09%
Total excluding ALL/AML	159	11	6.92%
Mortality			
ALL	169	11	6.51%
AML	291	0	0.00%
Solid tumors	54	0	0.00%
Transplant	68	1	1.47%
Autoimmune cytopenias	27	0	0.00%
Anti-NMDA encephalitis	4	0	0.00%
Other	13	0	0.00%
Total	626	12	1.92%

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TABLE 1 (Continued) Summary of toxicities of all grades in pediatric patients treated with bortezomib.

Indication	Evaluable patients	# of adverse events	% of patients experiencing complication, all grades
ALL/AML only	460	11	2.39%
Total excluding ALL/AML	166	1	0.60%

¹Incidents of reported infections, not individual patients.
Acute lymphoblastic leukemia (ALL); acute myeloid leukemia (AML); not reported (NR); anti-NMDA, Anti-N-methyl-d-aspartate.

data could not be extracted, and 1 trial included only adult (≥18 years old) patients. Thus, clinical trials registry did not yield additional analyzable data for this review.

Study types and treatment indications

The studies that met inclusion criteria included 11 clinical trials, 5 clinical studies (>10 patients), and 48 case series/case reports (≤10 patients) (Supplementary Tables S1–S3). Clinical trials included phase 1 (n = 9), phase 2 (n = 1), and phase 3 (n = 1) trials. Treatment indications included solid tumors, new/relapsed acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) (Supplementary Table S1).

Treatment indications for the clinical studies and case series/case reports included B-ALL, T-ALL, solid tumors, MM, antibody-mediated transplantation rejection, proliferative glomerulonephritis, autoimmune cytopenias after hematopoietic stem cell or intestinal transplant, refractory Evan’s syndrome, refractory TTP, refractory anti-NMDA encephalitis, complications secondary to ERT for Pompe’s disease, and heparin induced thrombocytopenia (Supplementary Tables S2, S3). BTZ was used as a single agent in 2 clinical trials and 2 case series but was more frequently administered with other drugs including chemotherapeutic agents and corticosteroids (Supplementary Tables S1–S3).

Peripheral neuropathy and other neurological AEs

Dose-dependent, reversible peripheral neuropathy (PN) is a known BTZ AE (Richardson et al., 2005; Argyriou et al., 2008; San Miguel et al., 2008; Moreau et al., 2011; Robak et al., 2018). In the BTZ drug insert, 38% of adult patients receiving BTZ experienced PN, with 11% experiencing ≥ grade 3 toxicity, leading to 8% of all patients to discontinue treatment (Takeda Pharmaceuticals, 2022). The overall incidence of PN in pediatric patients treated with BTZ was 8.56%, with 3.17% experiencing ≥ grade 3 toxicity (Tables 1, 2; Figure 2A). In young pediatric patients, defined as patients 8 years or younger, the overall incidence was 2.46% (Table 3). ALL and AML patients had a 10% incidence of PN. When ALL and AML were excluded, only 4.40% of pediatric patients and no young pediatric patients experienced PN (Tables 1, 3). Overall, pediatric patients experienced a lower incidence of PNs than adults, and PN improved or resolved completely after BTZ cessation.

Other neurological AEs have also been reported in adults. Headaches were reported in 15% of patients, with <1%

experiencing ≥ grade 3 toxicity. Transient ischemic attack, hemorrhagic stroke, coma, and Posterior Reversible Encephalopathy Syndrome were also reported although the incidences were not available (Takeda Pharmaceuticals, 2022). The overall incidence of other neurological AEs in pediatric patients treated with BTZ was 1.62%, with 1.69% of evaluable patients experiencing ≥ grade 3 toxicity (Tables 1, 2). Toxicities included headache, confusion, depressed level of consciousness, and seizures. In young pediatric patients, the overall incidence was 0.88% (Table 3). ALL and AML patients had a 1.2% incidence of other neurological AEs. When ALL and AML patients were excluded, 2.84% of pediatric patients and no young pediatric patients experienced other neurological AEs (Tables 1, 3; Figure 2A). Pediatric patients experienced fewer neurological AEs than adults.

Bone marrow toxicity

Bone marrow suppression has been reported for PIs in adults (Richardson et al., 2003a; Jagannath et al., 2004; Murai et al., 2014; Kim et al., 2015). Reported bone marrow toxicities in the BTZ clinical trial data for Mantle Cell Lymphoma and Multiple Myeloma included anemia, neutropenia/febrile neutropenia, thrombocytopenia, leukopenia, and lymphopenia (Takeda Pharmaceuticals, 2022). Pediatric studies reviewed in this systematic review similarly reported high incidences of bone marrow suppression.

The incidence of anemia in adults was 18%, with 6% experiencing ≥ grade 3 toxicity (Takeda Pharmaceuticals, 2022). Pediatric incidence was higher than adults at 35.56%, with 24.74% experiencing ≥ grade 3 toxicity (Tables 1, 2; Figure 2B). In young pediatric patients, the incidence of any grade anemia was 3.13% (Table 3). The majority of ALL patients (61.43%) experienced anemia. When ALL patients were excluded, 23.87% of pediatric patients and 3.45% of young pediatric patients experienced anemia (Tables 1, 3; Figure 2B).

The rate of neutropenia in adults was 15%, with 10% experiencing ≥ grade 3 toxicity (Takeda Pharmaceuticals, 2022). Pediatric incidence of neutropenia was higher at 46.62%, with 43.70% experiencing ≥ grade 3 toxicity (Tables 1, 2; Figure 2B). In young pediatric patients, the incidence of any grade neutropenia was 3.13% (Table 3). The majority of ALL patients (76.92%) experienced neutropenia. When patients with ALL were excluded, 24.20% of pediatric patients and 3.45% of young pediatric patients experienced neutropenia (Tables 1, 3; Figure 2B).

Febrile neutropenia, not described in the adult drug insert, was observed in 16.67% of pediatric patients, with 11.46% experiencing ≥ grade 3 toxicity (Tables 1, 2; Figure 2B). In young pediatric patients,

TABLE 2 Summary of grade 3+ toxicities in pediatric patients treated with bortezomib.

Indication	Evaluable patients	# of adverse events	% of patients experiencing complication, grade 3+
Peripheral Neuropathy			
ALL	159	8	5.03%
AML	0		
Solid tumors	52	2	3.85%
Transplant	67	0	0.00%
Autoimmune cytopenias	20	0	0.00%
Anti-NMDA encephalitis	4	0	0.00%
Other	13	0	0.00%
Total	315	10	3.17%
Other Neurological			
ALL	128	4	3.13%
AML	0		
Solid tumors	36	0	0.00%
Transplant	35	0	0.00%
Autoimmune cytopenias	20	0	0.00%
Anti-NMDA encephalitis	4	0	0.00%
Other	13	0	0.00%
Total	236	4	1.69%
Anemia			
ALL	70	38	54.29%
AML	0		
Solid tumors	51	7	13.73%
Transplant	32	2	6.25%
Autoimmune cytopenias	20	0	0.00%
Anti-NMDA encephalitis	4	0	0.00%
Other	13	0	0.00%
Total	190	47	24.74%
Neutropenia			
ALL	116	89	76.72%
AML	0		
Solid tumors	51	14	27.45%
Transplant	35	1	2.86%
Autoimmune cytopenias	20	0	0.00%
Anti-NMDA encephalitis	3	0	0.00%
Other	13	0	0.00%
Total	238	104	43.70%
Febrile Neutropenia			
ALL	70	17	24.29%

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TABLE 2 (Continued) Summary of grade 3+ toxicities in pediatric patients treated with bortezomib.

Indication	Evaluable patients	# of adverse events	% of patients experiencing complication, grade 3+
AML	0		
Solid tumors	22	1	4.55%
Transplant	35	0	0.00%
Autoimmune cytopenias	13	0	0.00%
Anti-NMDA encephalitis	4	0	0.00%
Other	13	0	0.00%
Total	157	18	11.46%
Thrombocytopenia			
ALL	117	92	78.63%
AML	0		
Solid tumors	51	14	27.45%
Transplant	30	1	3.33%
Autoimmune cytopenias	19	1	5.26%
Anti-NMDA encephalitis	4	0	0.00%
Other	13	0	0.00%
Total	234	108	46.15%
Leukopenia			
ALL	70	56	80.00%
AML	0		
Solid tumors	51	7	13.73%
Transplant	35	0	0.00%
Autoimmune cytopenias	18	0	0.00%
Anti-NMDA encephalitis	4	0	0.00%
Other	13	0	0.00%
Total	191	63	32.98%
Lymphopenia			
ALL	41	24	58.54%
AML	0		
Solid tumors	20	5	25.00%
Transplant	34	2	5.88%
Autoimmune cytopenias	20	0	0.00%
Anti-NMDA encephalitis	4	0	0.00%
Other	13	0	0.00%
Total	132	31	23.48%
Infection			
ALL	147	48	32.65%
AML	0		
Solid tumors	54	0	0.00%

(Continued on following page)

TABLE 2 (Continued) Summary of grade 3+ toxicities in pediatric patients treated with bortezomib.

Indication	Evaluable patients	# of adverse events	% of patients experiencing complication, grade 3+
Transplant	54	0	0.00%
Autoimmune cytopenias	13	0	0.00%
Anti-NMDA encephalitis	4	0	0.00%
Other	11	0	0.00%
Total	283	48	16.96%
Respiratory toxicities, excluding those attributable to infection			
ALL	117	3	2.56%
AML	0		
Solid tumors	21	0	0.00%
Transplant	31	0	0.00%
Autoimmune cytopenias	20	0	0.00%
Anti-NMDA encephalitis	4	0	0.00%
Other	13	0	0.00%
Total	206	3	1.46%
GI			
ALL	112	8	7.14%
AML	0		
Solid tumors	51	5	9.80%
Transplant	28	0	0.00%
Autoimmune cytopenias	12	0	0.00%
Anti-NMDA encephalitis	4	0	0.00%
Other	13	0	0.00%
Total	220	13	5.91%
Cardiac			
ALL	21	2	9.52%
AML	0		
Solid tumors	4	0	0.00%
Transplant	35	0	0.00%
Autoimmune cytopenias	20	0	0.00%
Anti-NMDA encephalitis	4	0	0.00%
Other	13	0	0.00%
Total	97	2	2.06%

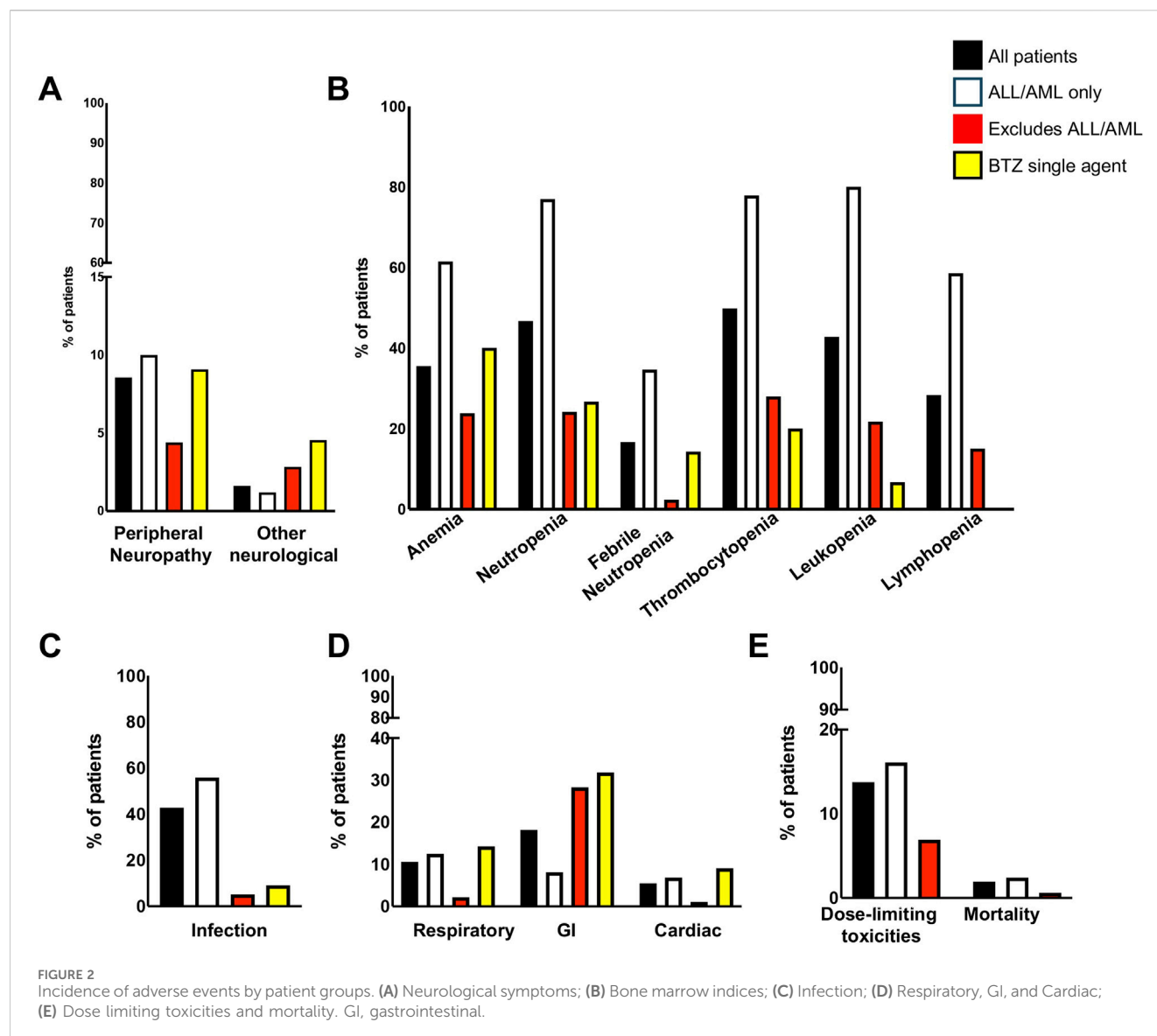
[†]Incidents of reported infections, not individual patients.

Acute lymphoblastic leukemia (ALL); acute myeloid leukemia (AML); not reported (NR); anti-NMDA, Anti-N-methyl-d-aspartate.

the incidence of any grade febrile neutropenia was 11.11% (Table 3). ALL and AML patients had a 34.65% incidence of febrile neutropenia. When patients with ALL and AML were excluded, 2.36% of all pediatric patients and no young pediatric patients experienced febrile neutropenia (Tables 1, 3; Figure 2B).

The incidence of thrombocytopenia in adults was 32%, with 25% experiencing \geq grade 3 toxicity (Takeda Pharmaceuticals, 2022).

Pediatric incidence was higher at 49.82%, with 46.15% experiencing \geq grade 3 toxicity (Tables 1, 2; Figure 2B). In young pediatric patients, the incidence of any grade thrombocytopenia was 6.25% (Table 3). The majority of ALL patients (77.87%) experienced thrombocytopenia. When patients with ALL were excluded, 28.03% of pediatric patients and 6.90% of young pediatric patients experienced thrombocytopenia (Tables 1, 3; Figure 2B).



While not reported in the combined adult drug insert (Takeda Pharmaceuticals, 2022), Robak et al. reported a rate of leukopenia in adults with previously untreated mantle cell lymphoma of 48% for all grades, with 43% experiencing \geq grade 3 toxicity (Robak et al., 2018). Pediatric incidence was comparable at 42.78%, with 32.98% experiencing \geq grade 3 toxicity (Tables 1, 2; Figure 2B). In young pediatric patients, the incidence of any grade leukopenia was 3.13% (Table 3). The majority of ALL patients (80%) experienced leukopenia. When patients with ALL were excluded, 21.77% of pediatric patients and 3.45% of young pediatric patients experienced leukopenia (Tables 1, 3; Figure 2B).

Similarly, Robak et al. found that 28% adults with previously untreated mantle cell lymphoma experienced lymphopenia, with 25% experiencing \geq grade 3 toxicity (Robak et al., 2018). Pediatric lymphopenia incidence was comparable, with an overall incidence of 28.36%, with 23.48% experiencing \geq grade 3 toxicity (Tables 1, 2; Figure 2B). In young pediatric patients, the incidence lymphopenia was 3.13% (Table 3). The majority of ALL patients (58.54%) experienced lymphopenia. When ALL patients were excluded,

15.05% of pediatric patients and 3.45% young pediatric patients experienced lymphopenia (Tables 1, 3).

Infections

Infection is a known BTZ AE in both adult and pediatric populations. Infectious complications including bacterial, viral, and fungal infections in BTZ-treated adults. Of these, only the incidence of pneumonia (8%) and herpes zoster (11%) were reported (Takeda Pharmaceuticals, 2022). Infection of any kind occurred in 42.81% of pediatric patients during BTZ treatment (Table 1; Figure 2C), with 16.96% experiencing \geq grade 3 toxicity (Table 2). Reported infection types ranged from mild sinusitis to severe life-threatening pulmonary aspergillosis, bacteremia or sepsis (Supplementary Tables S4–S6). In young pediatric patients, the incidence of any grade infection was 44.26% (Table 3). The majority of ALL and AML patients (55.87%) experienced lymphopenia. When these patients with ALL and AML were

TABLE 3 Summary of toxicities in pediatric patients age ≤ 8 treated with bortezomib.

Indication	Evaluable patients	# of adverse events	% of patients experiencing complication, all grades
Peripheral Neuropathy			
ALL	11	3	27.27%
AML	82	0	0.00%
Solid tumors	0		
Transplant	14	0	0.00%
Autoimmune cytopenias	5	0	0.00%
Anti-NMDA encephalitis	2	0	0.00%
Other	8	0	0.00%
Total	122	3	2.46%
ALL/AML only	93	3	3.23%
Total excluding ALL/AML	29	0	0.00%
Other Neurological			
ALL	3	0	0.00%
AML	81	1	1.23%
Solid tumors	0		
Transplant	14	0	0.00%
Autoimmune cytopenias	5	0	0.00%
Anti-NMDA encephalitis	2	0	0.00%
Other	8	0	0.00%
Total	113	1	0.88%
ALL/AML only	84	1	1.19%
Total excluding ALL/AML	29	0	0.00%
Anemia			
ALL	3	0	0.00%
AML	0		
Solid tumors	0		
Transplant	14	1	7.14%
Autoimmune cytopenias	5	0	0.00%
Anti-NMDA encephalitis	2	0	0.00%
Other	8	0	0.00%
Total	32	1	3.13%
ALL/AML only	3	0	0.00%
Total excluding ALL	29	1	3.45%
Neutropenia			
ALL	3	0	0.00%
AML	0		
Solid tumors	0		
Transplant	14	0	0.00%

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TABLE 3 (Continued) Summary of toxicities in pediatric patients age ≤8 treated with bortezomib.

Indication	Evaluable patients	# of adverse events	% of patients experiencing complication, all grades
Autoimmune cytopenias	5	0	0.00%
Anti-NMDA encephalitis	2	1	50.00%
Other	8	0	0.00%
Total	32	1	3.13%
ALL/AML only	3	0	0.00%
Total excluding ALL	29	1	3.45%
Febrile Neutropenia			
ALL	6	3	50.00%
AML	1	1	100.00%
Solid tumors	0		
Transplant	14	0	0.00%
Autoimmune cytopenias	5	0	0.00%
Anti-NMDA encephalitis	2	0	0.00%
Other	8	0	0.00%
Total	36	4	11.11%
ALL/AML only	7	4	57.14%
Total excluding ALL	29	0	0.00%
Thrombocytopenia			
ALL	3	0	0.00%
AML	0		
Solid tumors	0		
Transplant	14	1	7.14%
Autoimmune cytopenias	5	1	20.00%
Anti-NMDA encephalitis	2	0	0.00%
Other	8	0	0.00%
Total	32	2	6.25%
ALL/AML only	3	0	0.00%
Total excluding ALL	29	2	6.90%
Leukopenia			
ALL	3	0	0.00%
AML	0		
Solid tumors	0		
Transplant	14	0	0.00%
Autoimmune cytopenias	5	1	20.00%
Anti-NMDA encephalitis	2	0	0.00%
Other	8	0	0.00%
Total	32	1	3.13%
ALL/AML only	3	0	0.00%

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TABLE 3 (Continued) Summary of toxicities in pediatric patients age ≤8 treated with bortezomib.

Indication	Evaluable patients	# of adverse events	% of patients experiencing complication, all grades
Total excluding ALL	29	1	3.45%
Lymphopenia			
ALL	3	0	0.00%
AML	0		
Solid tumors	0		
Transplant	14	1	7.14%
Autoimmune cytopenias	5	0	0.00%
Anti-NMDA encephalitis	2	0	0.00%
Other	8	0	0.00%
Total	32	1	3.13%
ALL/AML only	3	0	0.00%
Total excluding ALL	29	1	3.45%
Infection^a			
ALL	11	2	18.18%
AML	82	48	58.54%
Solid tumors	0		
Transplant	14	3	21.43%
Autoimmune cytopenias	5	0	0.00%
Anti-NMDA encephalitis	2	0	0.00%
Other	8	1	12.50%
Total	122	54	44.26%
ALL/AML only	93	50	53.76%
Total excluding ALL/AML	29	4	13.79%
Respiratory toxicities, excluding those attributable to infection			
ALL	3	0	0.00%
AML	81	13	16.05%
Solid tumors	0		
Transplant	14	1	7.14%
Autoimmune cytopenias	5	0	0.00%
Anti-NMDA encephalitis	2	0	0.00%
Other	8	0	0.00%
Total	113	14	12.39%
ALL/AML only	84	13	15.48%
Total excluding ALL/AML	29	1	3.45%
GI			
ALL	11	2	18.18%
AML	1	0	0.00%
Solid tumors	0		

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TABLE 3 (Continued) Summary of toxicities in pediatric patients age ≤8 treated with bortezomib.

Indication	Evaluable patients	# of adverse events	% of patients experiencing complication, all grades
Transplant	14	2	14.29%
Autoimmune cytopenias	5	1	20.00%
Anti-NMDA encephalitis	2	0	0.00%
Other	8	0	0.00%
Total	41	5	12.20%
ALL/AML only	12	2	16.67%
Total excluding ALL/AML	29	3	10.34%
Cardiac			
ALL	0	0	9.52%
AML	81	1	1.23%
Solid tumors	0		
Transplant	14	0	0.00%
Autoimmune cytopenias	5	0	0.00%
Anti-NMDA encephalitis	2	0	0.00%
Other	8	0	0.00%
Total	110	1	0.91%
ALL/AML only	81	1	1.23%
Total excluding ALL/AML	29	0	0.00%
Dose-limiting toxicities			
ALL	11	0	0.00%
AML	82	12	14.63%
Solid tumors	0		
Transplant	14	0	0.00%
Autoimmune cytopenias	5	1	20.00%
Anti-NMDA encephalitis	2	0	0.00%
Other	8	0	0.00%
Total	122	13	10.66%
ALL/AML only	93	12	12.90%
Total excluding ALL/AML	29	1	3.45%
Mortality			
ALL	11	0	0.00%
AML	82	0	0.00%
Solid tumors	0		
Transplant	14	1	7.14%
Autoimmune cytopenias	5	0	0.00%
Anti-NMDA encephalitis	2	0	0.00%
Other	8	0	0.00%
Total	122	1	0.82%

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TABLE 3 (Continued) Summary of toxicities in pediatric patients age ≤8 treated with bortezomib.

Indication	Evaluable patients	# of adverse events	% of patients experiencing complication, all grades
ALL/AML only	93	0	0.00%
Total excluding ALL/AML	29	1	3.45%

^aIncidents of reported infections, not individual patients.
Acute lymphoblastic leukemia (ALL); acute myeloid leukemia (AML); not reported (NR); anti-NMDA, Anti-N-methyl-d-aspartate.

excluded, 5.03% of pediatric patients and 13.79% of young pediatric patients experienced infection (Tables 1, 3; Figure 2C).

Respiratory toxicity

Respiratory toxicity is a rare but potentially serious complication of BTZ in adults, ranging in severity from asthma-like symptoms or dyspnea to rapidly progressive pulmonary fibrosis (Saglam et al., 2020), though the incidence of milder respiratory toxicity in BTZ-treated adults treated is unknown. Respiratory events reported in pediatric studies included hypoxia, respiratory failure, and ARDS, which were pooled into a single category because of differences in reporting across studies. The overall incidence of respiratory toxicity was 10.62%, with 1.46% experiencing ≥ grade 3 toxicity (Tables 1, 2; Figure 2D). In young pediatric patients, the incidence was 12.39% (Table 3). ALL and AML patients had a 12.50% incidence of respiratory AEs. When patients with AML and ALL were excluded, 2.20% of pediatric patients and 3.45% of young pediatric patients experienced respiratory toxicity (Tables 1, 3; Figure 2D).

Gastrointestinal toxicity

Gastrointestinal (GI) toxicities are known AEs of BTZ treatment owing to its effect on rapidly dividing GI epithelial cells. In BTZ-treated adults, 20% had anorexia, 28% had vomiting, and 46% experienced diarrhea; 7%, 2%, and 4% experienced these ≥ grade 3 toxicities, respectively (Takeda Pharmaceuticals, 2022). GI toxicities for pediatrics were categorized differently than in adults (Takeda Pharmaceuticals, 2022) and thus direct comparison was not possible. Nevertheless, pediatric incidence of GI AE appeared lower. Reported GI toxicities in pediatric patients included abdominal pain, typhlitis/colitis, nausea, vomiting, anorexia, diarrhea, mucositis, enterocolitis, ileus, and pancreatitis. When multiple GI toxicities occurred in a single patient, they are reported as a single GI AE. The overall incidence of GI AEs was 18.18%, with 5.91% experiencing ≥ grade 3 toxicity (Tables 1, 2; Figure 2D). In young pediatric patients, the rate of any grade GI toxicity was 12.20% (Table 3). ALL and AML patients had a 8.13% incidence of GI toxicities. When patients with ALL and AML were excluded, 28.30% of pediatric patients and 10.34% of young pediatric patients experienced GI toxicity (Tables 1, 3; Figure 2D).

Cardiac toxicities

Cardiac toxicity has been described in the drug insert as a potential BTZ AE. The adult incidence of treatment-related cardiac conditions is at 8% and includes new or worsening heart failure, decreased left ventricular

ejection fraction, ischemic symptoms/myocardial infarction, arrhythmias, pericarditis, and pericardial effusion (Takeda Pharmaceuticals, 2022). Pediatric incidence of cardiac AEs was 5.51%, with 2.06% experiencing ≥ grade 3 toxicity (Tables 1, 2; Figure 2D). Toxicities reported in pediatric patients included heart failure, left ventricular systolic dysfunction, and hypotension. In young pediatric patients, the overall incidence was 0.91% (Table 3). ALL and AML patients had a 6.82% incidence of cardiac toxicities. When ALL and AML were excluded, 1.1% of pediatric patients and no young pediatric patients experienced cardiac AEs (Tables 1, 3; Figure 2D). In summary, pediatric patients experienced a lower incidence of cardiac AEs than adults.

Dose limiting toxicities (DLTs)

DLT occurred in 13% of adults treated with BTZ, with the most common reasons for discontinuation being PN (5%) and diarrhea (3%) (Takeda Pharmaceuticals, 2022). Pediatric incidence of DLT was comparable at 13.78% (Table 1; Figure 2E). Reasons for discontinuation, reduction, or delay in dose were often not reported. The most frequently specified DLT was GI toxicity (0.65%), thrombocytopenia (0.65%), or PN (0.65%). In young pediatric patients, the incidence of DLT was lower than adults at 10.66% (Table 3). ALL and AML patients had a 16.09% incidence of dose-limiting toxicities. When patients with ALL and AML were excluded, the incidence of DLT was even lower at 7.01% of all pediatric patients and 3.45% of young pediatric patients (Tables 1, 3; Figure 2E).

Deaths

Deaths while on BTZ therapy were rare. Adult mortality rate during BTZ treatment (with or without other concurrent treatment) ranged from 0.17% to 4% (Takeda Pharmaceuticals, 2022; Bringham et al., 2018). Pediatric mortality rate was 1.92% (Table 1; Figure 2E), with an incidence for young pediatric patients of 0.82% (Table 3). The most common cause of on-therapy mortality was infection. Infections were predominantly fungal (5/8) and occurred in the context of broad immunosuppression with co-therapy of combinations of vincristine, dexamethasone, pegylated L-asparaginase, doxorubicin, intrathecal methotrexate, and/or intrathecal triple chemotherapy (methotrexate, cytarabine, methylprednisolone or hydrocortisone) (Supplementary Table S4). Of the 12 pediatric deaths reported to be possibly related to BTZ therapy, 11 occurred in patients with ALL (Table 3; Figure 2E). One death (0.60%) occurred after heart transplantation due to renal and pulmonary complications (Morrow et al., 2012).

Toxicities when bortezomib was used as a single agent

Of the 64 articles used in this systematic review, 4 articles (2 clinical trials and 2 case series/reports) described the use of BTZ as a single agent (Supplementary Tables S1–S3). This cohort of patients had higher neurological toxicities (4.55%) and GI toxicities (31.82%) (Figure 2; Supplementary Table S7). Interestingly, they had similar incidence of toxicities relative to non-ALL or AML patients receiving multi-therapy.

Certainty of evidence and risk of bias

A significant limitation of this systematic review is a paucity of blinded pediatric studies of BTZ. The majority of studies (48/64) included in this analysis were case reports or case series ≤ 10 patients and did not have a systematic framework for evaluating AEs. The risk of researcher influence or selection bias in cases chosen for publication was also possible.

Discussion

Our systematic review demonstrates that the BTZ toxicity profile for pediatric patients differs from adults. Adult BTZ toxicities affect the nervous, cardiac and pulmonary, GI systems, and cause bone marrow suppression and infections. Pediatric patients had similar or higher incidence of bone marrow suppression and infection, but decreased incidence of neurological, cardiac, pulmonary, and GI AEs.

Evaluation of BTZ's safety profile in pediatric patients is complicated by its use in conjunction with multiple chemotherapeutic agents and in immunosuppressed ALL, AML and organ transplantation patients. Patients meeting these criteria comprised approximately 50% of pediatric study patients (Table 1; Supplementary Tables S4–S6). Non-ALL or AML patients experienced lower incidence of PN, pulmonary toxicities, and infectious complications, and demonstrates that BTZ toxicity is likely exacerbated by co-morbidities (Table 1). Pediatric patients receiving BTZ as a single agent had toxicities similar to non-ALL or AML patients receiving multiple therapies.

PN is one of the most common and dose-limiting toxicity in adults treated with BTZ (Argyriou et al., 2008; Yamamoto and Egashira, 2021; Yang et al., 2024), affecting up to 38% of adult patients (Takeda Pharmaceuticals, 2022). Although poorly understood, it is believed that BTZ affects glial cells, causing axonal degeneration, impairing axonal transport, and inducing oxidative stress and inflammation in the peripheral nervous system (Yamamoto and Egashira, 2021; Yang et al., 2024). Pediatric patients treated with BTZ had a 4-fold lower incidence of PN when compared to adults (8.6%, vs. 38%, Table 1). When ALL pediatric patients were excluded, the incidence of PN was nearly 9-fold lower (4.4% Table 1). Moreover, PN in pediatric patients was generally low-grade and reversible. There was a higher incidence of PN in ALL and AML patients, compared to non-ALL or AML indications. When BTZ was used as a single agent, the PN incidence was as high as the ALL and AML patients (Supplementary Table S7). The majority of this cohort were treated for oncologic indications. This may suggest that oncologic patients inherently are more sensitive to neurotoxic effects of BTZ. A phase 1 clinical trial of ALL patients using BTZ and vincristine reported 83% of patients with grade 2 PN (Iguchi et al., 2017), while it

was not reported in another clinical trial of ALL patients in which BTZ was used as a single agent (Horton et al., 2007). These data suggest that pediatric patients had more favorable risk profile of PN compared to adults. A recent paper by Joshi et al. found that pediatric ALL patients who experienced PN during vincristine treatment tolerated a switch to BTZ with equivocal efficacy and significantly less PN (Joshi et al., 2019). Our study confirmed that the AE profile of BTZ may be more favorable than vincristine for ALL patients.

Pediatric patients receiving BTZ also have low incidence of cardiopulmonary and GI toxicities. Adult cardiovascular toxicities were dose-dependent and included new or worsening heart failure and ischemic heart disease (Takeda Pharmaceuticals, 2022). Pediatric cardiac AEs were less common than adults and included hypotension, left ventricular dysfunction, and heart failure. GI toxicities for both adult and pediatric patients included nausea, vomiting, diarrhea and were lower in pediatric patients compared to adults. Incidence of adult pulmonary AEs were not reported in the drug insert (Takeda Pharmaceuticals, 2022); pediatric pulmonary AEs included hypoxia, respiratory failure, and ARDS.

Several factors may contribute to the higher incidence of cardiac and GI toxicities observed in adults relative to pediatric patients. Research in neurodegenerative diseases has found that the proteasomal degradation activity decreases with age (Rousseau and Bertolotti, 2018). This age-induced proteasome instability may contribute to the worsening of the AEs to PIs (Georgiopoulos et al., 2023), which may explain why pediatric patients experience less BTZ-induced neurological, cardiac and GI AEs. Additionally, adults are more likely to have pre-existing comorbidities that increase the risk of developing BTZ-induced AEs such as cardiotoxicity and neuropathy (Georgiopoulos et al., 2023). Neuropathy-inducing comorbidities such as diabetes mellitus are more common in adults and can increase the risk of BTZ-induced PN (Lanzani et al., 2008; Bruna et al., 2010). Neuropathy secondary to multiple myeloma has been shown to increase the likelihood of developing neuropathy following BTZ treatment. These data may explain why pediatric patients have lower incidence of PN from BTZ treatment (Meregalli et al., 2015). Similarly, cardiovascular risk factors, which have a higher prevalence in older patients, increase the risk of BTZ-induced cardiotoxicity (Kistler et al., 2017). Decline of the proteasome activity, differences in BTZ indication, and age-associated comorbidities all may contribute to the lower rate of neurological, cardiac and GI toxicities in pediatric patients.

Pediatric patients treated with BTZ experience high incidence of bone marrow suppression including anemia, neutropenia, and thrombocytopenia ranging from 17% to 50% (Table 1). When pediatric patients with ALL were excluded, the pediatric AE incidences were decreased to $<30\%$, comparable to adults. In contrast, ALL and AML patients had rates of bone marrow suppression up to 80%, which puts them at higher risk for infection. ALL/recurrent ALL and AML patients in these published studies were on multi-agent regimens which confounds the contribution of BTZ in bone marrow suppression in this patient population (Table 1). Horton et al. concluded that while BTZ might have exacerbated thrombocytopenia, the rates were not different from historical controls of ALL patients without BTZ treatment (Horton et al., 2019). Pediatric leukopenia and lymphopenia incidence were comparable to adults (Robak et al., 2018) (Tables 1–3).

The most significant pediatric BTZ toxicity is infection (42.8%), which occurred in most deaths potentially attributable to BTZ (Table 1)

(Horton et al., 2007; Messinger et al., 2010; Yeo et al., 2016; Bertaina et al., 2017; Iguchi et al., 2017; Kaspers et al., 2018; Hasegawa et al., 2019; Horton et al., 2019; Roy et al., 2019; August et al., 2020; Colunga-Pedraza et al., 2020; Ravichandran et al., 2021). Infection is a serious concern during treatment with BTZ and is especially common in patients with blood malignancies. A high rate of infection may be expected in heavily pretreated and immunosuppressed patient groups (Takeda Pharmaceuticals, 2022). The frequency and severity of infections observed in BTZ-treated pediatric ALL patients were comparable to those observed in studies of recurrent ALL patients receiving standard reinduction chemotherapy (Horton et al., 2019; August et al., 2020). These studies suggest that the risk of infection attributable specifically to BTZ may be over-estimated in ALL and AML patients concurrently treated with other chemotherapeutic agents. These results confirm ALL and AML patients are at increased infectious risks from their underlying primary disease and immunosuppressive effects of concurrent therapies in addition to BTZ. Infectious toxicities in pediatric patients treated with BTZ for non-ALL/or was much lower (5%) (Table 1). Nevertheless, bone marrow suppression remains the major toxicity that is experienced in non-ALL or AML pediatric patients.

This study had major shortcomings. The decision to include publications with toxicity data for patients ≤ 18 years of age disqualified many clinical trials from analysis. This decision was based on older teenager and young adults (18–21) having similar physiology to adults and thus experienced toxicities may not reflect true pediatric response to BTZ. For this same reason, we further stratified patients into young pediatric patients (≤ 8 years old) when data was available for analysis. Our data demonstrated that younger pediatric patients tolerated BTZ better than older pediatric patients. This is consistent with other reports that younger ALL pediatric patients (≤ 14 years) have decreased treatment-related toxicities compared to adolescents and young adults using pediatric protocols (Gupta et al., 2021; Janardan and Miller, 2023). The majority of source publications were smaller clinical studies (>10 patients) or case report/series (≤ 10 patients) and thus more anecdotal than well-controlled clinical trials. This uneven distribution of patient population may confound our findings that ALL and AML patients experience higher incidence of AEs. Nevertheless, this review endeavored to include pediatric patients undergoing BTZ treatment for both oncologic and non-oncologic indications with a goal to comprehensively review BTZ toxicities in pediatric patients. Even though there is a lack of well-controlled clinical trials for pediatric patients undergoing BTZ treatment (with or without concurrent therapies) for non-oncologic indications, the collective experience in the medical literature for this population should be reviewed and analyzed as BTZ is being used for a widening range of indications in the pediatric setting.

Conclusion

Our systematic review demonstrates that BTZ is acceptable for use in pediatric patients. Pediatric patients with ALL or AML had higher risks for AEs and \geq grade 3 AEs. PN, GI, and pulmonary toxicities were lower in pediatric patients than adults. In contrast, bone marrow suppression and infection were the major AEs for pediatric patients and occurred at rates comparable to those in adults. Finally, dose-limiting toxicities were comparable to the adult experience (Blaney et al., 2004; Kaspers et al.,

2018; August et al., 2020). Due to the high incidence of bone marrow suppression and infection in ALL and AML patients, antibiotic and anti-fungal prophylaxis while on BTZ therapy is recommended to minimize infection/sepsis risks. While infections occurred at a lower rate for non-ALL or AML patients, bone marrow suppression remained the main toxicity that is experienced. Therefore, antibiotic and anti-fungal prophylaxis should also be considered for non-ALL or AML patients on BTZ. As BTZ targets pathologic cells with abnormal protein accumulation, using doses lower than standard oncologic doses in non-malignant and non-transplantation pediatric patients may also provide efficacy while minimizing AEs.

Author contributions

ZL: Investigation, Formal Analysis, Methodology, Data curation, Writing – review and editing, Writing – original draft, Validation. AC: Data curation, Formal Analysis, Validation, Writing – original draft. SK: Validation, Writing – review and editing, Data curation. CS: Validation, Methodology, Writing – review and editing, Supervision, Conceptualization. JW: Conceptualization, Supervision, Validation, Writing – review and editing, Methodology, Formal Analysis.

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Conflict of interest

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fphar.2025.1661493/full#supplementary-material>

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