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Adverse Events in Adults with Relapsed or Refractory Acute Lymphoblastic Leukemia (ALL): A Literature Review of Recent Clinical Trials

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Abstract

Background: With the introduction of new therapy options for adult patients with relapsed or refractory (R/R) acute lymphoblastic leukemia (ALL), a better understanding of existing toxicity profiles is needed.

Methods: A systematic literature review was conducted to summarize the toxicity profiles in clinical trials using chemotherapeutic regimens, tyrosine kinase inhibitor (TKI)-based approaches in Philadelphia chromosome-positive (Ph+) and Philadelphia chromosome-negative (Ph-) R/R ALL, or other targeted therapies. Seventeen eligible articles were identified that reported toxicity profiles. We grouped adverse events into the following categories: hematological, infectious, gastrointestinal, cardiovascular/renal/hepatic, and neurological, stratified by treatment type. Treatment-related or early/induction mortality was also summarized.

Results: With cytotoxic chemotherapy and its combinations, hematological adverse events were the most common, affecting virtually all patients, followed by infections, which were reported in most patients. Neurologic toxicity was the most common adverse event associated with liposomal vincristine. TKI-based treatments showed a distinct safety profile compared with the chemotherapies. Although hematological adverse events still represented the most common toxicity, infections were less common with TKI-based therapies (9-18%) than with chemotherapies (56-100%). Nausea, vomiting, and diarrhea were the predominant gastrointestinal adverse events after receipt of TKIs, whereas mucositis appeared to be more characteristic of cytotoxic chemotherapy.

Conclusions: This paper provides a systematic review of the safety profile of current standard chemotherapy for adults with R/R Ph- or Ph+ ALL. Overall, documentation of adverse events was highly variable across the studies, precluding direct comparisons or pooling of results. However, this systematic literature review is the first to summarize and quantify the toxicity profiles of mainly chemotherapeutic and TKI-based regimens for adult patients with R/R ALL, providing a baseline for comparison with emerging therapies.

Keywords: Acute Lymphoblastic Leukemia; Relapsed; Refractory; Adverse events; Toxicity; Clinical trials

Introduction

Acute lymphoblastic leukemia (ALL) is a rare disease with an overall incidence rate of 1.4/100,000 persons per year in the United States [1]. Approximately 85-90% of adult patients with ALL achieve a complete remission (CR) with current induction chemotherapy regimens [2]. With improved management strategies, including better risk stratification and optimized therapeutic tools such as pediatric-based chemotherapeutic regimens, targeted therapies such as tyrosine kinase inhibitors (TKIs), and allogeneic hematopoietic stem cell transplantation (allo-HSCT), overall survival rates of 40-50% in adult ALL patients are possible [2,3].

Despite these improvements, at least one-third of patients with standard-risk ALL and two-thirds with high-risk ALL experience a relapse [3]. In patients experiencing relapses, overall survival is much poorer, with only 7% surviving 5 years [4]. Survival was shown to be significantly better when allo-HSCT was performed after first relapse in CR compared to later CR or with detectable leukemia (56 ± 7% vs. 39 ± 11% vs. 20 ± 5%, respectively, for three-year survival) [3]. Some of the prognostic factors for improved outcomes after allo-HSCT are achieving CR, shorter time to CR achievement, lower number of previous treatments, and having less comorbidity at the time of allo-HSCT [3-5]. The most important goal of an effective salvage regimen is inducing CR with minimal toxicity to allow patients to proceed with allo-HSCT.

In the past decade, new innovative therapy options have emerged for the treatment of adult R/R ALL. New formulations, such as

liposomes (synthetic vesicles), can deliver higher concentrations of chemotherapy to leukemia targets without increased toxicity [6]. Moreover, there are new approaches using targeted therapies such as imatinib against BCR-ABL in patients with Philadelphia chromosome-positive (Ph+) ALL [7-9]. Second-generation TKIs can induce cytogenetic responses in a substantial percentage of ALL patients who fail imatinib [10].

New immunoconjugates targeting CD19 and CD22 have also shown promising results in patients with relapsed ALL [11,12]. Two newer immunotherapeutic agents, the bispecific T-cell-engaging antibody construct blinatumomab and *chimeric* antigen receptor-modified *T cells,* have demonstrated improved CR rates in adult patients with R/R ALL, with a toxicity profile different from that of prior chemotherapy regimens [13,14].

Currently, a systematic overview and synthesis of the toxicity profiles of different established salvage regimens for R/R ALL is lacking. Such an overview is needed to provide a better understanding of the existing toxicity profiles with the introduction of these new therapy options. Therefore, we conducted a systematic literature review of toxicity profiles among clinical trials using conventional chemotherapeutic regimens, TKI-based approaches in Ph+ ALL, or other newer therapies for R/R ALL.

Methods

Literature selection criteria

To maximize the comparability of study designs and populations, we restricted articles to those describing phase II, III, or IV clinical trials of chemotherapies or TKIs exclusively in adult patients with R/R ALL. We excluded studies of HSCT, as well as those including any patients with lymphoma or leukemia other than ALL or exclusively T-cell ALL. To ensure more stable statistical results, articles were further restricted to those that included at least 20 patients. Phase 0/I trials, observational studies, case reports, letters, commentaries, editorials, guidelines, reviews, and studies of animals, tissues, or cells were also excluded.

Literature search

We searched MEDLINE, accessed via PubMed, for English-language articles published from January 2002 through December 2013 that reported the occurrence of adverse events in adults with R/R ALL. The search was conducted using the following search string: acute AND (lymphoblastic OR lymphocytic OR lymphoid) AND (leukemia OR leukaemia) AND (relaps* OR refractor* OR resistan* OR recur* OR salvage OR rescue) AND adult* AND (trial OR regimen). We also identified additional potentially relevant articles from the reference lists of retrieved articles.

Two investigators independently reviewed titles and abstracts of identified articles, as well as the full text of articles that were selected for closer evaluation. From an initial pool of 731 potentially eligible articles we included 17 eligible articles, after excluding reviews, observational studies, radiation studies, Phase 0 and I trials, and other ineligible studies (Figure 1).

Data extraction

The following adverse event categories were found to be routinely reported: neurological, infectious, infusion-related, hematological, bleeding/coagulation-related, cardiovascular, renal, gastrointestinal, hepatic, and pulmonary, as well as overall and cause-specific mortality.

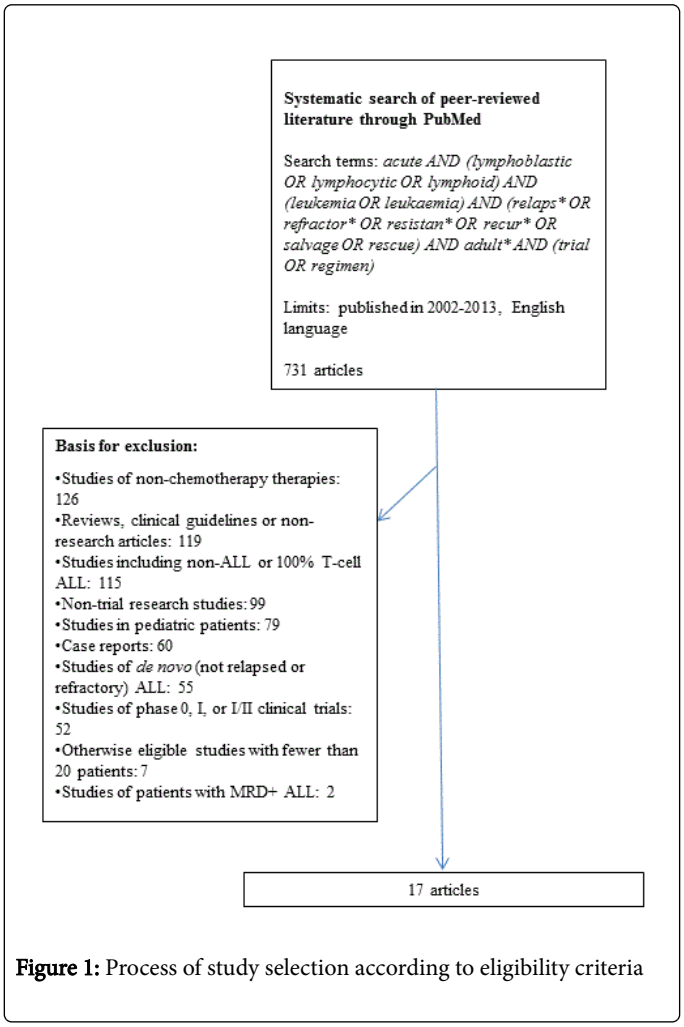

Figure 1: Process of study selection according to eligibility criteria

These categories, including specific adverse events within each category, were included in this review. In addition, we also searched for information on tumor lysis syndrome, capillary leak syndrome, cytokine release syndrome, and alopecia, but these adverse events were not reported. Information on study design, patient characteristics, treatment regimen, and ascertainment and frequency of adverse events was extracted into a structured spreadsheet and independently checked for accuracy by at least one other investigator.

The main outcome of interest was the frequency of each adverse event in each study. We grouped some specific adverse events, as reported by the original investigators, into the following categories: "bleeding/hemorrhage," "bacterial infection/sepsis," "oral toxicity," "nausea/vomiting," "gastrointestinal toxicity," "arrhythmia/atrial or ventricular rhythm alterations," "heart failure/cardiac insufficiency," "renal toxicity," "hemorrhagic cystitis/bladder hemorrhage," "hepatic toxicity," "neurologic events," and "polyneuropathy." Specific adverse events included in each combined category are listed in the included tables. If an article presented information on more than one adverse event in a category or reported on more than one treatment group, we provide a frequency range for each category. Otherwise, we present adverse events as reported by the original investigators. We provide frequencies of adverse events for all grades combined or unspecified

grades, for grades 1–2, and for grades 3–4, as reported by the original investigators. Adverse events that occurred after HSCT were excluded.

Treatment-related mortality (TRM) or early/induction mortality was also an outcome of interest. Some investigators explicitly described particular deaths as treatment-related, whereas others described deaths as occurring early or during induction, without specific attribution to treatment procedures. However, because early/induction mortality could be due to acute treatment-related toxicity, and because TRM was not consistently documented or defined across articles, we combined these two categories for reporting and refer to this grouping as "TRM/early mortality". If investigators specifically attributed certain deaths to disease progression, we did not include these as TRM or early/induction mortality. Deaths that occurred after HSCT were excluded.

Results

Of the 17 articles (describing 16 study populations) included in this systematic literature review (Table 1), all were phase II trials except for one phase III trial [10]. Twelve articles described patients with primarily Philadelphia chromosome-negative (Ph-) R/R ALL. Nine studies used combination chemotherapy regimens [15-23], and one used vincristine sulfate liposome injection monotherapy [6]. Two overlapping studies [11,24] reported treatment with inotuzumab ozogamicin, with the earlier study reporting the experiences of the first 49 patients treated, and the later one including results of 90 patients. Across all studies, the sample size ranged from 20 to 135 patients. Five studies of TKI treatments in patients with Ph+ R/R ALL were also included in this review [10,25-28] and are described separately (Table 1). In these studies, the sample size ranged from 22 to 84 patients.

First Author	Phase	Sample Size	Treatment	Disease status or prior lines of therapy	Treatment-Related Mortality or Early/Induction Mortality, Attribution Not Specified		
					All Causes	Infection	Other
Camera et al. [16]	II	135	Cytarabine and idarubicin	Refractory: 21% First relapse: 73% Second relapse: 6% Prior transplant: 2%	11.9% during or soon after chemotherapy	9.6%	2.2% hemorrhage 1.5% gastrointestinal hemorrhage 0.7% cerebral hemorrhage 1.4% heart failure
Karbasian-Esfahani et al. [20]	II	20	Cytarabine and idarubicin	First relapse: 60% Second or later relapse: 40%	---	---	---
Reman et al. [21]	II	38	Amsacrine, cytarabine, and etoposide	First relapse: 100%	---	2.6%	---
Di Bona et al. [18]	II	36	Mitoxantrone and methotrexate	Primary refractory: 8% First relapse: 92% Prior transplant: 14%	13.9%	11.1%	2.8% hemorrhage
Specchia et al. [22]	II	23	Fludarabine, cytarabine, and idarubicin	Primary refractory: 22% First relapse: 78%	---	4.3% bacterial infection (*Pseudomonas aeruginosa*) during aplasia	---
Candoni et al. [17]	II	25	Liposomal daunorubicin and cytarabine	First relapse: 68% Second or later relapse: 32% Prior transplant: 36%	4% within 30 days after reinduction	4% septic shock (*Pseudomonas* sp., *Enterococcus sp,*. and *Listeria monocytogenes*)	---
Giebel et al. [19]	II	50	Fludarabine, cytarabine, and mitoxantrone	Primary refractory: 26% Secondary refractory: 10% First relapse: 56% Second or later relapse: 8%	16% early (during aplasia)	12.0% sepsis	4.0% cardiac complications

				Prior transplant: 26%			
Tedeschi et al. [23]	II	25	Cytarabine and idarubicin	Primary refractory: 48% First relapse: 52% Prior transplant: 4%	0.0% during aplasia	---	---
Advani et al. [15]	II	36	Clofarabine and cytarabine	Refractory: 25% First relapse: 56% Second or later relapse: 19% Prior transplant: 6%	19.4% 27.8% during protocol treatment	8.3% 2.8% sepsis	2.8% pleural effusion 2.8% disseminated intravascular coagulation 2.8% hypotension/renal failure/cardiac arrhythmia 2.8% multiorgan failure 2.8% pulmonary/renal failure
O'Brien et al. [6]	II	65	Vincristine sulfate liposomes	Number of prior lines of therapy: 2: 49% 3: 37% ≥4: 14% Prior transplant: 48%	23.1% during treatment period 12.3% during 30-day induction	3.1% septic shock (during treatment period)	3.1% cardiac arrest 3.1% respiratory distress (during treatment period)
Kantarjian et al. [11], Kantarjian et al. [24]	II	49, 90	Inotuzumab ozogamicin	Salvage 1: 32% Salvage 2: 38% ≥Salvage 3: 30% Prior transplant: 11%	4.4% overall within 4 weeks 4.0% single-dose within 4 weeks 4.9% weekly-dose within 4 weeks		2.0% CNS bleed on day 21 of single-dose (induction)
Tyrosine kinase inhibitors							
Wassmann et al. [27]	II	22	Imatinib	Primary refractory: 73% First relapse: 18% Second relapse: 9% Prior transplant: 5%	---	---	---
Wassmann et al. [28]	II	68	Imatinib	Primary refractory: 37% First relapse: 41% Second or later relapse: 19% Complete remission 1: 3% Prior transplant: 35%	---	---	---
Ottmann et al. [26]	II	36	Dasatinib	Not specified, but 100% had prior treatment with imatinib Prior transplant: 42%	---	---	---
Lilly et al. [10]	III	84	Dasatinib	Not specified, but 100% had	1.2%	---	---

				prior treatment with imatinib Prior transplant: 27%			
Ottmann et al. [25]	II	41	Nilotinib	Primary refractory: 2% Secondary refractory: 5% First relapse: 51% Second relapse: 37% Third relapse: 2% Minimal residual disease with evolving relapse: 2%	27% during treatment or within 28 days		

Table 1: Study description and treatment-related mortality in adults with relapsed or refractory acute lymphoblastic leukemia (ALL) by treatment category.

Treatment-related or early/induction mortality

Table 1 provides data on TRM/early mortality. In studies of patients receiving combination chemotherapy regimens, TRM/early mortality of all causes ranged from 0% to 27.8% [15-19,23]. In studies that reported causes of TRM/early mortality [16,18,19] the majority of early deaths were attributed to infection, which had a TRM/early mortality that ranged from 2.6% to 12% [15-19,21,22]. Other causes of TRM/early mortality included hemorrhage, cardiac problems, pleural effusion, disseminated intravascular coagulation, renal failure, multiorgan failure, and respiratory distress [15,16,18,19].

Three studies of two patient populations reported TRM/early mortality in relation to treatment with newer therapies, namely liposomal vincristine and inotuzumab ozogamicin [6,11,24]. Of 65 patients receiving liposomal vincristine, 23.1% (n=15) experienced TRM/early mortality during the treatment period, with specific causes of death including septic shock, cardiac arrest, and respiratory distress [6,11]. Among patients receiving a single dose of inotuzumab ozogamicin once every 3-4 weeks, 4.0% (n=2/49) experienced TRM/early mortality within 4 weeks, including one death (2%) from central nervous system (CNS) bleeding, while 4.9% (n=2/41) of those receiving weekly doses of inotuzumab ozogamicin died within 4 weeks [11,24].

Only two studies reported TRM/early mortality among Ph+ R/R ALL patients receiving TKIs [10,25]. Lilly et al. [10] reported a TRM rate of 1.2% (n=1/84), but did not specify cause of death. Ottmann et al. [25] observed that 27% (n=11/41) of patients receiving nilotinib died during treatment or within 28 days of starting treatment, but the authors report "no death was suspected to be related" to the study drug.

Hematological toxicity

Hematological adverse events were the most frequently occurring toxicities of salvage chemotherapy regimens (Table 2), although they occurred less frequently in patients receiving vincristine sulfate liposome [6]. With the exception of patients in the studies by Advani et al. [15] and Di Bona et al. [18], where hematological toxicity was not reported in detail, all patients (100%) treated with standard combination chemotherapy regimens experienced cytopenias of various grades. The median time to neutrophil recovery>0.5×10^9/L ranged from 17 [23] to 27 days [16,21]. The median time to reach platelet count>20×10^9/L ranged from 17 [23] to 23 days [22], and to >50×10^9/L ranged from 20 [20] to 34 days [16,17]. In contrast to most salvage therapies for which occurrence of hematological adverse events was very high, among patients receiving vincristine sulfate liposome, neutropenia occurred in only 17% of patients, including 1.5% (n=1/65) grades 1–2, 8% (n=5/65) grade 3, and 8% (n=5/65) grade 4 [6]. The overall incidence of thrombocytopenia of all grades was 9%, including grade 3 in 3% (n=2/65) and grade 4 in 6% (n=4/65) [6]. In 49 patients treated with inotuzumab ozogamicin [11,24], the reported incidence of thrombocytopenia and neutropenia was stratified by platelet and absolute granulocyte counts, respectively, prior to starting treatment. In patients with absolute granulocyte counts ≥ 1×10^9/L before therapy, the incidence of grades 3 and 4 neutropenia was 12% (n=3/25) and 76% (n=19/25), respectively. The incidence of neutropenia was not reported for patients with lower absolute granulocyte counts before therapy. Patients who had platelet counts>$100,000\times10^9$/L before treatment experienced thrombocytopenia of grades 1–2, 3, and 4 at frequencies of 33% (n=2/6), 17% (n=1/6), and 17% (n=1/6), respectively. In patients whose platelet counts were <$100,000\times10^9$/L, the incidence of grades 3 and 4 thrombocytopenia was 27% (n=3/11) and 73% (n=8/11), respectively [11,24]. Median time to neutrophil or platelet count recovery was not reported.

For other hematologic adverse events, only O'Brien et al. [6] reported occurrence of anemia, with frequencies of 12% (n=8/65) for all grades and 5% (n=3/65) for grades 3–4. Grades 3–4 coagulation abnormalities were described in 3% (n=1/36) of patients by Advani et al. [15]. Bleeding or hemorrhage, likely to be associated with thrombocytopenia, was reported by Specchia et al. [22] (9% [n=2/23] grades 1–2 and 4% [n=1/23] grades 3–4), Candoni et al. [17] (0% [n=0/25] grade 2 and 0% [n=0/25] grades 3–4), and Giebel et al. [19] (46% [n=23/50] grades 1–2 and 4% [n=2/50] grades 3–4).

Adverse event	Study	Treatment	Frequency (%) of adverse event*		
			All grades	Grades 1-2	Grades 3-4
Cytopenia (including neutropenia, thrombocytopenia and/or anemia)	Reman et al. [21]	Amsacrine, cytarabine, and etoposide	100%		
	Candoni et al. [17]	Liposomal daunorubicin and cytarabine	100%		100%
	Giebel et al. [19]	Fludarabine, cytarabine, and mitoxantrone	100%		
Neutropenia	Karbasian-Esfahani et al. [20]	Cytarabine and idarubicin	100%		
	Specchia et al. [22]	Fludarabine, cytarabine, and idarubicin	100%		
	Tedeschi et al. [23]	Cytarabine and idarubicin			100%
	Kantarjian et al. [11]	Inotuzumab ozogamicin			88%
	O'Brien et al. [6]	Vincristine sulfate liposomes	17%	2%	15%
Anemia	O'Brien et al. [6]	Vincristine sulfate liposomes	12%	8%	5%
Thrombocytopenia	Karbasian-Esfahani et al. [20]	Cytarabine and idarubicin	100%		
	Tedeschi et al. [23]	Cytarabine and idarubicin	100%		100%
	Kantarjian et al. [11]	Inotuzumab ozogamicin	67-100%	0-33%	33-100%
	O'Brien et al. [6]	Vincristine sulfate liposomes	9%	3%	6%
Coagulation abnormality	Advani et al. [15]	Clofarabine and cytarabine			6%
Bleeding/ hemorrhage	Specchia et al. [22]	Fludarabine, cytarabine and idarubicin	13%	9%	4%
	Candoni et al. [17]	Liposomal daunorubicin and cytarabine		0% (grade 2)	0%
	Giebel et al. [19]	Fludarabine, cytarabine and mitoxantrone	50%	46%	4%

Table 2: Frequency of hematological adverse events in adult patients with relapsed or refractory acute lymphoblastic leukemia (ALL) receiving current treatments.
* Studies that are not included above did not report on these AEs.

Infectious toxicity

Because patients with R/R ALL are intrinsically immunosuppressed from the underlying hematological disease, as well as chemotherapy-associated cytopenia, infections represent a common toxicity of Ph-ALL salvage treatment (Table 3). Among studies that reported on all infections combined or febrile neutropenia as an indicator of general infection, the incidence of grades 3–4 infection ranged from 3% (n=2/65 with febrile neutropenia) [6] to 56% (n=20/36) [15]. Overall infection of all grades was reported in up to 100% of patients (n=38/38) [21].

Some authors reported on specific infections in more detail by differentiating among bacterial, viral, and fungal infections, typically for all grades combined. The incidence of bacterial infection or sepsis of all grades ranged from 16% (n=8/49) [11] to 60% (n=12/20) [20] (with one study reporting a grades 3–4 incidence of 28% [n=7/25] [23]); that of viral infection of all grades ranged from 4% (n=2/49) [11] to 20% (n=5/25) [17]; and that of fungal infection of all grades ranged from 2% (n=1/49) [11] to 15% (n=3/20) [20] (with one study reporting a grades 3–4 incidence of 4% [n=2/25] [23]).

Adverse event	Study	Treatment	Frequency (%) of adverse event*		
			All grades	Grades 1-2	Grades 3-4
Infection	Reman et al. [21]	Amsacrine, cytarabine and etoposide	100%	61%	37%
	Di Bona et al. [18]	Mitoxantrone and methotrexate			0-17%

	Specchia et al. [22]	Fludarabine, cytarabine and idarubicin	83%	57%	22%
	Candoni et al. [17]	Liposomal daunorubicin and cytarabine	56%		
	Giebel et al. [19]	Fludarabine, cytarabine and mitoxantrone	92%	34%	46%
	Advani et al. [15]	Clofarabine and cytarabine			56%
Febrile neutropenia	Specchia et al. [22]	Fludarabine, cytarabine and idarubicin	57%		
	Kantarjian et al. [11]	Inotuzumab ozogamicin	16%		
	O'Brien et al. [6]	Vincristine sulfate liposomes	8%	5%	3%
Bacterial and/or fungal infection	Camera et al. [16]	Cytarabine and idarubicin	21%		
	Giebel et al. [19]	Fludarabine, cytarabine and mitoxantrone			48%
Bacterial infection/sepsis	Karbasian-Esfahani et al. [20]	Cytarabine and idarubicin	60%		
	Specchia et al. [22]	Fludarabine, cytarabine and idarubicin	17%		
	Candoni et al. [17]	Liposomal daunorubicin and cytarabine	52%		
	Tedeschi et al. [23]	Cytarabine and idarubicin			28%
	Kantarjian et al. [11]	Inotuzumab ozogamicin	16%		
Viral infection	Candoni et al. [17]	Liposomal daunorubicin and cytarabine	20%		
	Kantarjian et al. [11]	Inotuzumab ozogamicin	4%		
Fungal infection	Karbasian-Esfahani et al. [20]	Cytarabine and idarubicin	15%		
	Specchia et al. [22]	Fludarabine, cytarabine and idarubicin	4%		
	Candoni et al. [17]	Liposomal daunorubicin and cytarabine	4%		
	Tedeschi et al. [23]	Cytarabine and idarubicin			8%
	Kantarjian et al. [11]	Inotuzumab ozogamicin	2%		
Pneumonia	Tedeschi et al. [23]	Cytarabine and idarubicin			24%
	Kantarjian et al. [11]	Inotuzumab ozogamicin	18%		

Table 3: Frequency of infectious adverse events in adult patients with relapsed or refractory acute lymphoblastic leukemia (ALL) receiving current treatments.
* Studies that are not included above did not report on these AEs.

Gastrointestinal toxicity

The most common gastrointestinal toxicities associated with chemotherapy regimens were oral toxicity/mucositis, nausea, and vomiting (Table 4). Regimens containing cytarabine had an incidence of oral toxicity/mucositis ranging from 15% to 65% for grades 1–2 and 5% to 13% for grades 3–4 [16-20,22-24]. Candoni et al. [17] reported grade 1 nausea and vomiting in the majority (n ≥ 13) of 25 patients treated with liposomal daunorubicin and cytarabine. Grades 2–3 mucositis was reported in 36% (n=9/25) of patients, among whom 56% (n=5/9) were found to have herpes simplex virus reactivation. The authors reported that "no other significant gastrointestinal toxicities were observed." Grades 3–4 cutaneous/mucosal toxicity was seen in 19% (n=7/36) of patients in the Di Bona et al. [18] study who received the first course of methotrexate and mitoxantrone, and 11% (n=2/18) of those who received the second, lower-dose course [18]. The incidence of grades 3–4 mucositis was 0% (n=0/41) for those who received weekly doses of inotuzumab and 2% (n=1/49) for those who received a single dose once every 3-4 weeks [24]. Some degree of nausea and vomiting occurred with all chemotherapy regimens, although inotuzumab resulted in the lowest rate (0% [n=0/49] with a single dose, 12% [n=5/41] with weekly doses) [24]. Other gastrointestinal toxicity also occurred commonly with the combination chemotherapy regimens. Constipation occurred often with liposomal vincristine (34% [n=22/65] for all grades, including 3% [n=2/65] grade 3) [6], while the frequency of gastrointestinal toxicity was lowest with inotuzumab (0%–6% [n=3/49] for all grades, depending on dose schedule and specific type of gastrointestinal toxicity) [24].

Adverse event	Study	Treatment	Frequency (%) of adverse event*		
			All grades	Grades 1-2	Grades 3-4
Oral toxicity (terms include oral toxicity, mucositis, and cutaneous/ mucosal toxicity)	Camera et al. [16]	Cytarabine and idarubicin	20%	15%	5%
	Karbasian-Esfahani et al. [20]	Cytarabine and idarubicin		>0%	5%
	Di Bona et al. [18]	Mitoxantrone and methotrexate			11-19%
	Specchia et al. [22]	Fludarabine, cytarabine and idarubicin	78%	65%	13%
	Candoni et al. [17]	Liposomal daunorubicin and cytarabine		36% (grades 2-3)	
	Giebel et al. [19]	Fludarabine, cytarabine and mitoxantrone	56%	48%	8%
	Tedeschi et al. [23]	Cytarabine and idarubicin			12%
	Kantarjian et al. [24]	Inotuzumab ozogamicin	0-2%	0-0%	0-2%
Nausea/vomiting	Karbasian-Esfahani et al. [20]	Cytarabine and idarubicin	>0%	>0%	0%
	Specchia et al. [22]	Fludarabine, cytarabine, and idarubicin	17%	17%	0%
	Candoni et al. [17]	Liposomal daunorubicin and cytarabine	"majority"	"majority" (grade 1)	0%
	Giebel et al. [19]	Fludarabine, cytarabine and mitoxantrone	80%	70%	10%
	Tedeschi et al. [23]	Cytarabine and idarubicin			16%
	Kantarjian et al. [24]	Inotuzumab ozogamicin	0-12%	0-12%	0-0%
	O'Brien et al. [6]	Vincristine sulfate liposomes	11-22%	11-22%	0-0%
Gastrointestinal toxicity (terms include gastrointestinal toxicity, gastroenteric, diarrhea, constipation, colitis, typhlitis, abdominal pain, decreased appetite, anorexia)	Camera et al. [16]	Cytarabine and idarubicin			0.7%
	Karbasian-Esfahani et al. [20]	Cytarabine and idarubicin	>0%	>0%	0%
	Reman et al. [21]	Amsacrine, cytarabine, and etoposide	100%	76%	24%
	Di Bona et al. [18]	Mitoxantrone and methotrexate			31-33%
	Candoni et al. [17]	Liposomal daunorubicin and cytarabine			0%
	Giebel et al. [19]	Fludarabine, cytarabine, and mitoxantrone	10-30%	8-24%	2-6%
	Tedeschi et al. [23]	Cytarabine and idarubicin			8%
	Advani et al. [15]	Clofarabine and cytarabine			3-6%
	Kantarjian et al. [24]	Inotuzumab ozogamicin	0-6%	0-6%	0-0%
	O'Brien et al. [6]	Vincristine sulfate liposomes	6-34%	5-31%	2-3%

Table 4: Frequency of gastrointestinal adverse events in adult patients with relapsed or refractory acute lymphoblastic leukemia (ALL) receiving current treatments.

* Studies that are not included above did not report on these AEs.

Cardiac toxicity

Cardiac toxicity secondary to chemotherapy is usually related to the cumulative dose of anthracycline, which most patients with ALL receive during their front-line therapy. The reported incidence of grades 3–4 cardiac toxicity was 0% in four of five chemotherapy salvage regimens [17,20,21,23] and 8–11% in the fifth (n=3/36 and 2/18 for the first and second course, respectively, of mitoxantrone and

methotrexate) [18] (Table 5). Candoni et al. [17] reported "no early or late cardiac toxicity" among 25 patients when liposomal daunorubicin was combined with cytarabine. However, one patient (who did not receive prior anthracyclines; 4%) developed transient atrial fibrillation that resolved completely.

Adverse event	Study	Treatment	Frequency (%) of adverse event*		
			All grades	Grades 1-2	Grades 3-4
Cardiovascular					
Cardiac toxicity	Karbasian-Esfahani et al. [20]	Cytarabine and idarubicin	0%	0%	0%
	Reman et al. [21]	Amsacrine, cytarabine and etoposide	100%	100%	0%
	Di Bona et al. [18]	Mitoxantrone and methotrexate			8-11%
	Candoni et al. [17]	Liposomal daunorubicin and cytarabine			0%
	Tedeschi et al. [23]	Cytarabine and idarubicin	0%	0%	0%
Arrhythmia/ atrial or ventricular rhythm alterations	Camera et al. [16]	Cytarabine and idarubicin	2%	0%	2%
	Candoni et al. [17]	Liposomal daunorubicin and cytarabine	4%	4%	0%
	Giebel et al. [19]	Fludarabine, cytarabine and mitoxantrone	18%	18%	0%
	Advani et al. [15]	Clofarabine and cytarabine			3%
Heart failure/cardiac insufficiency	Camera et al. [16]	Cytarabine and idarubicin	3%	0%	1%
	Giebel et al. [19]	Fludarabine, cytarabine and mitoxantrone	12%	2%	6%
Restrictive cardiomyopathy	Advani et al. [15]	Clofarabine and cytarabine			3%
Hypotension	Advani et al. [15]	Clofarabine and cytarabine			8%
	Kantarjian et al. [24]	Inotuzumab ozogamicin	15-27%	15-24%	0-2%
Renal					
Renal toxicity (terms include renal toxicity, renal failure, increase in creatinine)	Karbasian-Esfahani et al. [20]	Cytarabine and idarubicin	0%	0%	0%
	Reman et al. [21]	Amsacrine, cytarabine and etoposide	100%	100%	0%
	Di Bona et al. [18]	Mitoxantrone and methotrexate			3-11%
	Specchia et al. [22]	Fludarabine, cytarabine and idarubicin	9%	9%	0%
	Giebel et al. [19]	Fludarabine, cytarabine and mitoxantrone	8%	8%	0%
	Advani et al. [15]	Clofarabine and cytarabine			8%
Hemorrhagic cystitis/bladder hemorrhage	Specchia et al. [22]	Fludarabine, cytarabine and idarubicin	4%		
	Tedeschi et al. [23]	Cytarabine and idarubicin			4%
Hepatic					
Hepatic toxicity (including liver dysfunction, liver damage, increased bilirubin, increased aminotransferase)	Camera et al. [16]	Cytarabine and idarubicin	14%	14%	0%
	Karbasian-Esfahani et al. [20]	Cytarabine and idarubicin			5%
	Reman et al. [21]	Amsacrine, cytarabine and etoposide	100%	84%	16%
	Di Bona et al. [18]	Mitoxantrone and methotrexate			8-11%
	Specchia et al. [22]	Fludarabine, cytarabine and idarubicin	17-26%	17-26%	0-0%
	Candoni et al. [17]	Liposomal daunorubicin and cytarabine			0%
	Giebel et al. [19]	Fludarabine, cytarabine and mitoxantrone	28%	20%	8%

	Tedeschi et al. [23]	Cytarabine and idarubicin			4%
	Advani et al. [15]	Clofarabine and cytarabine			3%
	Kantarjian et al. [24]	Inotuzumab ozogamicin	5-57%	5-55%	0-5%
Hypoalbuminemia	Kantarjian et al. [24]	Inotuzumab ozogamicin	0-2%	0-2%	0-0%
Periportal fibrosis with hyperbilirubinemia	Kantarjian et al. [11]	Inotuzumab ozogamicin	4% ("mild to moderate")		

Table 5: Frequency of cardiovascular, renal, and hepatic adverse events in adult patients with relapsed or refractory acute lymphoblastic leukemia (ALL) receiving current treatments.
* Studies that are not included above did not report on these AEs.

Hypotension was reported as an infusion-related toxicity in two studies [15,24]. There was an 8% (n=3/36) incidence of grades 3–4 hypotension in patients treated with clofarabine [15]. In patients treated with a single dose of inotuzumab once every 3-4 weeks, 24% (n=12/49) developed grades 1–2 hypotension and 2% (n=1/49) developed grades 3–4 [24]. When inotuzumab was given weekly, the incidence of grades 1–2 hypotension was 15% (n=6/41) and that of grades 3–4 was 0% [24].

Renal toxicity

Grades 3–4 renal toxicity was reported in 3–11% of patients (n=1/36 first course, n=2/18 second course) treated with mitoxantrone and methotrexate [18], 8% (n=3/36) of patients treated with clofarabine and cytarabine [15], and 0% of patients in four studies of combination salvage chemotherapy [19-22] (Table 5). Grades 1–2 renal toxicity was reported in 100% of patients receiving cytarabine, amsacrine and etoposide [21] and 8% to 9% in other combination chemotherapy studies [19,22].

Hepatic toxicity

Hepatic toxicity was observed in all 38 patients who received cytarabine, amsacrine, and etoposide [21], with incidences of 84% (n=32) for grades 1–2 and 16% (n=6) for grades 3–4 (Table 5). Candoni et al. [17] reported no "significant" liver toxicity when cytarabine was combined with liposomal daunorubicin (n=0/25). Kantarjian et al. [24] reported 22–55% grades 1–2 (n=9/41 weekly dose, n=27/49 single dose) and 2–5% grades 3–4 liver toxicity (n=2/41 and 1/49) as evidenced by increased aminotransferase levels, and 5–24% grades 1–2 (n=2/41 and 12/49) and 0–4% grades 3–4 (n=0/41 and 2/49) as evidence by increased bilirubin with inotuzumab [24].

Neurological toxicity

Unspecified neurological toxicity occurred in all 38 patients (97% [n=37] grades 1–2, 3% [n=1] grade 3) treated with cytarabine, amsacrine, and etoposide (Table 6) [21]. Among patients treated with liposomal vincristine [6], the incidence of all nervous system disorders was 63% (n=41/65), including 19% (n=12/65) grade 3 and 2% (n=1/65) grade 4. For peripheral neuropathy-related events in particular, the incidence was 23% (n=15/65) for grade 3 and 2% (n=1/65) for grade 4, including peripheral neuropathy (15% grade 3), hypoesthesia (2% grade 3), paresthesia (2% grade 3), areflexia (2% grade 3), hyporeflexia (0% grade 3), limb pain, and motor weakness.

Adverse event	Study	Treatment	Frequency (%) of adverse event*		
			All grades	Grades 1-2	Grades 3-4
Neurologic events (term includes neurologic events, neurological events, CNS toxicity)	Karbasian-Esfahani et al. [20]	Cytarabine and idarubicin	0%	0%	0%
	Reman et al. [21]	Amsacrine, cytarabine and etoposide	100%	97%	3%
	Di Bona et al. [18]	Mitoxantrone and methotrexate			3-6%
	Specchia et al. [22]	Fludarabine, cytarabine and idarubicin	0%	0%	0%
	Giebel et al. [19]	Fludarabine, cytarabine and mitoxantrone	8%	6%	2%
	Advani et al. [15]	Clofarabine and cytarabine			6%
	O'Brien et al. [6]	Vincristine sulfate liposomes	63%	43%	20%
Headache	Kantarjian et al. [24]	Inotuzumab ozogamicin	2-2%	2-2%	0-0%
Polyneuropathy	O'Brien et al. [6]	Vincristine sulfate liposomes	8-31%	8-23%	0-25%

(terms include peripheral neuropathy, hypoesthesia, paresthesia, areflexia, hyporeflexia, limb pain, motor weakness)					

Table 6: Frequency of neurological adverse events in adult patients with relapsed or refractory acute lymphoblastic leukemia (ALL) receiving current treatments.
* Studies that are not included above did not report on these AEs.

In other studies with available data, the incidence of grades 3–4 neurologic events, which were nonspecifically classified as "neurologic," "neurological," or "central nervous system" toxicity, ranged from 0% (n=0/20 and 0/23) [20,22] to 6% (n=1/18 and 2/36) [15,18-20,22].

Toxicity of TKI-based regimens in Ph+ R/R ALL

TKI-based regimens used in patients with Ph+ R/R ALL showed a different pattern of adverse events in comparison with salvage chemotherapy regimens (Table 7). Whereas hematological events remained the most common adverse events, infections were less frequent, albeit based on limited data [10,26,27]. Among 36 patients receiving dasatanib, grades 3–4 febrile neutropenia occurred in 11% (n=4) [26]. As reported by Lilly et al. [10], 9–18% of patients treated with dasatanib (n=7/40 receiving 140 mg once daily, n=4/44 receiving 70 mg twice daily) experienced infection of all grades, and 5–8% (n=3/40 and 2/44) experienced grades 3–4 infection. In the same study, 7–13% of patients (n=3/44 and 5/40) had grades 3-4 febrile neutropenia [10].

Among all five studies of TKIs, grades 3–4 hematological adverse events included neutropenia (range: 41–72%), thrombocytopenia (range: 19–88%), leukocytopenia (range: 54–70%), and anemia (range: 26–47%) [10,25-28]. Lilly et al. [10] reported hemorrhage in 15% (n=6/40) of patients receiving 140 mg dasatinib once daily and in 16% (n=7/44) receiving 70 mg dasatanib twice daily, with 9–10% grades 1–2 and 5–7% grades 3–4. Grades 1-2 non-CNS and non-gastrointestinal-associated hemorrhage were seen in 9–10% of the patients [10].

Approximately one-third of patients experienced at least one gastrointestinal adverse event [10,25-27]. Diarrhea, nausea, and vomiting were the main gastroenterological toxicities, and appeared to be mostly grades 1–2. The incidence of grades 1–2 diarrhea ranged from 5% (n=1/22) [27] to 30% (n=12/40) [10]; the incidence of grades 1–2 nausea ranged from 20% (n=9/44) to 41% (n=9/22) [27]; and the incidence of grades 1–2 vomiting ranged from 11% (n=4/36) [26] to 20% (n=8/40) [10]. Mucositis was not reported. Few other adverse events were reported in more than one study of TKIs. One was grades 3–4 hepatic toxicity, which occurred in 5% (n=1/22) of patients receiving imatinib [27] and 10–15% of patients (n=4/41 with decreased albumin, 6/41 with hyperbilirubinemia) receiving nilotinib [25]. Headache of all grades (mostly grades 1–2, where reported) occurred in 7–10% of patients receiving dasatinib (n=3/44 with 70 mg twice daily, n=4/40 with 140 mg once daily) [10], 14% of patients (n=5/36) in another trial of dasatinib, and 17% (n=7/41) of patients receiving nilotinib [25]. Pleural effusion was reported in 18–32% of patients (n=7/40 with 140 mg once daily, n=14/44 with 70 mg twice daily; 3–14% grades 3–4) receiving dasatanib in one trial [10], and 19% (n=7/36; 3% grades 3–4) in another [26]. In the same two dasatanib trials, the incidence of dyspnea was 10–23% (n=4/40 and 10/44; 0–3% grades 3–4) in one [10] and 14% (n=5/36; 3% grades 3–4) in the other [26].

Adverse event	Study	Treatment	Frequency (%) of adverse event*		
			All grades	Grades 1-2	Grades 3-4
Hematologic					
Neutropenia	Wassmann et al. [27]	Imatinib			41%
	Wassmann et al. [28]	Imatinib			50%
	Ottmann et al. [26]	Dasatinib			72%
	Lilly et al. [10]	Dasatinib	79-85%	7-18%	67-72%
	Ottmann et al. [25]	Nilotinib			44%
Anemia	Ottmann et al. [26]	Dasatinib			47%
	Lilly et al. [10]	Dasatinib	98-100%	61-64%	36-36%
	Ottmann et al. [25]	Nilotinib			26%
Thrombocytopenia	Wassmann et al. [27]	Imatinib			88%
	Wassmann et al. [28]	Imatinib			19%

	Ottmann et al. [26]	Dasatinib			78%
	Lilly et al. [10]	Dasatinib	88-92%	21-28%	60-72%
	Ottmann et al. [25]	Nilotinib			63%
Leukocytopenia	Ottmann et al. [26]	Dasatinib			64%
	Lilly et al. [10]	Dasatinib	81-85%	12-31%	54-70%
Hemorrhage	Lilly et al. [10]	Dasatinib	15-16%	9-10%	5-7%
Non-CNS, non-GI hemorrhage	Lilly et al. [10]	Dasatinib	9-10%	7-10%	0-2%
Infections					
Infection	Lilly et al. [10]	Dasatinib	9-18%	5-10%	5-8%
Febrile neutropenia	Ottmann et al. [26]	Dasatinib	11%	0%	11%
	Lilly et al. [10]	Dasatinib	7-13%	0-0%	7-13%
Fungal infection	Wassmann et al. [27]	Imatinib	0%		
Gastrointestinal					
Anorexia	Lilly et al. [10]	Dasatinib	8-11%	8-11%	0-0%
Nausea/vomiting	Wassmann et al. [27]	Imatinib		14-41%	
	Ottmann et al. [26]	Dasatinib	11-22%	11-22%	0%
	Lilly et al. [10]	Dasatinib	18-28%	16-25%	0-5%
	Ottmann et al. [25]	Nilotinib	15-29%		5%
All grades					
Gastritis	Lilly et al. [10]	Dasatinib	0-10%	0-8%	0-3%
Diarrhea	Wassmann et al. [27]	Imatinib		5%	
	Ottmann et al. [26]	Dasatinib	31%	23%	8%
	Lilly et al. [10]	Dasatinib	27-35%	22-30%	5-5%
	Ottmann et al. [25]	Nilotinib	19%		
GI bleeding	Lilly et al. [10]	Dasatinib	5-11%	0-5%	5-7%
Cardiovascular					
Pericardial effusion	Lilly et al. [10]	Dasatinib	2-3%	2-3%	0-0%
Pulmonary					
Pleural effusion	Ottmann et al. [26]	Dasatinib	19%	17%	3%
	Lilly et al. [10]	Dasatanib	18-32%	15-18%	3-14%
Pulmonary edema	Lilly et al. [10]	Dasatinib	0-7%	0-5%	0-2%
Dyspnea	Ottmann et al. [26]	Dasatinib	14%	11%	3%
	Lilly et al. [10]	Dasatinib	10-23%	8-23%	0-3%
Hepatic					
Elevated liver enzymes, hyperbilirubinemia, decreased albumin	Wassmann et al. [27]	Imatinib			5%
	Ottmann et al. [25]	Nilotinib			10-15%

Neurological			0%	0%	0%
CNS hemorrhage	Lilly et al. [10]	Dasatinib	0-2%	0-2%	0-0%
Headache	Ottmann et al. [26]	Dasatinib	14%	14%	0%
	Lilly et al. [10]	Dasatinib	7-10%	5-10%	0-2%
	Ottmann et al. [25]	Nilotinib	17%		
Bifrontal cerebral hygromas	Wassmann et al. [28]	Imatinib	3%		

Table 7: Frequency of adverse events in adult patients with Philadelphia chromosome+ relapsed or refractory acute lymphoblastic leukemia (ALL) receiving tyrosine kinase treatments.
*Studies that are not included above did not report on these AEs.

Pulmonary edema was also reported in a dasatanib trial in 0–7% of patients (n=0/40 with 140 mg once daily, n= 3/44 with 70 mg twice daily; 0–2% grades 3–4) [10]. Neurological adverse events reported in one study each were bifrontal cerebral hygromas in two (3%) of 68 imatinib-treated patients, both of whom also had grades 3–4 thrombocytopenia [28]; and grades 1–2 CNS hemorrhage in one (2%) of 44 patients treated with 70 mg twice daily dasatinib [10,25].

Conclusions

This paper provides a systematic review of the safety profile of current standard chemotherapy for adults with R/R Ph- or Ph+ ALL. The objective of this review was to provide a baseline to put into context the safety profiles of newer, mainly immunological treatments for R/R ALL. To the best of our knowledge, this is the first systematic assessment of adverse events in R/R ALL.

With chemotherapy, the most consistently reported common adverse events were hematologic, followed by infections. Mucositis and gastrointestinal toxicity also tended to be common with chemotherapy. For inotuzumab, an agent targeted to the B-cell antigen CD22, severe hematological toxicity was observed in approximately 90% of patients with available data, hepatic toxicity was present in about half, and up to half experienced infectious complications (assuming each reported infection occurred in a different patient). In about one-fifth of patients receiving inotuzumab, grades 1-2 hypotension was also observed, although it was less frequent with weekly administration than with a single dose every three weeks. Therapy with liposomal vincristine was associated with nervous system disorders in 63% of the patients, including peripheral neuropathy-associated complaints in 23%, making neurologic toxicity the most frequent adverse event reported with this treatment. Neurotoxicity was reported by one other study where patients were treated with amascrine, cytarabine, and etoposide [21].

TKI-based treatments showed a different safety profile. While hematological adverse events still represented the most common toxicity, infections were less common, with a frequency of 9-18% with TKI-based therapies, versus 56-100% with chemotherapies. Compared with standard chemotherapeutic treatment approaches, gastrointestinal adverse events were relatively frequent with TKIs, although the pattern appeared to be different, with nausea, vomiting, and diarrhea being the predominant adverse events after receipt of TKIs, and mucositis apparently being more characteristic of cytotoxic chemotherapy. As observed among chronic myeloid leukemia treated with TKIs [29,30] pleural effusions and dyspnea were also observed in up to one-third of TKI-treated R/R ALL patients.

Documentation of adverse events was highly variable across the studies. Most likely, because of the unmet need in R/R ALL, the focus of studies is generally on efficacy parameters. In evaluating treatment options for a potentially fatal disease, adverse event reporting can perhaps be seen as an ancillary concern. We do not imply strong criticism of clinical trial investigators; nevertheless, in view of the emergence of newer therapeutic tools, such as immunotherapeutic approaches that appear to feature a different toxicity profile (with predominantly immunologic, neurologic, and some hepatic toxicity but less hematologic, gastrointestinal, cardiac, and renal toxicity) [14,15], systematic reporting of adverse events has greater importance in the context of treatment decisions, risk-benefit assessment, and overall evaluation of new therapies.

During the article review process, several sources of variability in adverse event reporting became apparent. Across publications, no standard format was used for reporting adverse events. Different adverse events were selected for reporting and the degree of detail varied in the classification of particular adverse events or event categories. Some studies reported adverse events in broad categories (e.g., neurological), thereby obscuring the frequency of specific adverse events (e.g., headache) within those categories. Grade of severity was not always reported, and if so, grades were sometimes reported separately or combined in various ways (e.g., grades 1–2 or grades ≤ 3). In many studies, it was not clear whether certain adverse events were counted in multiple overlapping categories (e.g., infections and bacterial infections or sepsis). In a few cases, exact data were replaced by qualitative phrases, such as "a majority." Some, but not all, investigators attributed certain adverse events to the treatment under evaluation, and reporting of "suspected unexpected serious adverse reactions" was completely lacking. Investigators generally did not specify whether adverse events attributed to disease progression were or were not systematically reported, but practices may have varied. Due to differences in study populations and eligibility criteria, treatment regimens, and methods of defining, ascertaining and reporting adverse events, comparisons across studies should be made with caution. Quantitative summaries (e.g., meta-analyses or pooled analyses) were not considered feasible or appropriate in this situation.

Thus, although the primary intent of this literature review was not to evaluate the quality and completeness of adverse reporting, it revealed a need for more systematic and thorough reporting of adverse events. Clearly, we are not the first to emphasize the importance of more systematic documentation of adverse events in clinical trial

literature. Others [31-34] have previously stressed the need for transparent and comprehensive adverse event reporting, and developed a consensus statement for adverse event reporting in clinical trials. However, as recently shown by Sivendran et al. [34], many randomized oncology trials do not adequately fulfill consensus standards for reporting, even when published in journals that endorse these standards.

The main limitations of this literature review result from the non-systematic reporting of adverse events, as outlined above. When a study did not report the frequency of a given adverse event, it was not clear whether the event did not occur, occurred but was not recorded by the study investigators, or occurred and was recorded but was not reported in the publication. Most studies were single-arm clinical trials of limited size and, therefore, also of limited statistical precision. The literature search strategy and study eligibility criteria that we used may limit the scope of our findings. However, in view of the heterogeneity and other inherent limitations of the data, and based on our experience that use of other literature databases does not substantially augment search results, we designed the search strategy and study eligibility criteria to maximize the comparability of studies. Finally, the frequencies of toxicities reported in clinical trial participants may not reflect the frequencies of toxicities experienced by patients in real-world settings, as patients are selected for clinical trials based on numerous inclusion and exclusion criteria.

In conclusion, this systematic literature review is the first to summarize and quantify the toxicity profile of standard therapeutic options for adult patients with R/R ALL. In addition, this review reveals the challenges of summarizing and interpreting the available data on adverse events associated with these treatments. In light of the development of newer immunological treatment approaches with unique toxicity profiles, and the need to make informed treatment decisions based on considerations of both efficacy and safety, more systematic and transparent adverse event reporting is needed in clinical trials. With the hope that new therapies will bring an improved outcome and more opportunities for HSCT for R/R ALL patients, a focus on improving patient co-morbidities and reducing adverse events is emerging. This review provides a basis for evaluating the safety profiles for new emerging treatments.

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