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Research paper

Blinatumomab administered concurrently with oral tyrosine kinase inhibitor therapy is a well-tolerated consolidation strategy and eradicates measurable residual disease in adults with Philadelphia chromosome positive acute lymphoblastic leukemia

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ABSTRACT

Incorporation of ABL-targeted oral tyrosine kinase inhibitors (TKIs) into frontline therapeutic regimens has improved outcomes for adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph + ALL). However, patients with persistent minimal residual disease (MRD) exhibit increased risk of relapse. Combining consolidative chemotherapy with TKIs may increase rates of infectious complications, organ toxicity, hospitalization, and non-relapse mortality. Blinatumomab has demonstrated single-agent activity in patients with relapsed B-ALL or persistent MRD, including Ph + B-ALL. We have used blinatumomab concomitantly with commercially available TKIs as consolidative therapy to spare toxicities of conventional chemotherapy. We evaluated 11 adults with previously treated Ph + B-ALL who received blinatumomab concurrent with TKI (ponatinib, n = 5; dasatinib, n = 4; nilotinib, n = 1; imatinib, n = 1) to eradicate MRD or sustain MRD-negativity. Eight of 9 patients with MRD achieved BCR-ABL1 negativity (complete molecular response, CMR) after a median of one cycle; 2/2 patients without measurable disease durably maintained CMR. Cytokine release syndrome (all grade 1–2) was observed in 3/11 patients; one patient experienced transient grade 1 neurologic toxicity. Transient grade 2 transaminitis was observed in 6/11 patients, including 4/5 recipients of blinatumomab + ponatinib. This small series suggests blinatumomab + TKI is a safe and effective consolidation strategy for patients with Ph + ALL to achieve or maintain CMR.

1. Introduction

Philadelphia chromosome positive B-cell acute lymphoblastic leukemia (Ph + ALL) is a biologically and clinically distinct subtype of ALL, accounting for 20–30% of adult ALL cases and comprising a greater proportion of ALL cases among older adults. [1–3] This cytogenetic aberration significantly impacts prognosis and treatment. The prognosis of adults with Ph + ALL has historically been dismal, with marked reduction in event free survival (EFS) and overall survival (OS) compared with adults with Ph-negative ALL. [2,4] Incorporation of BCR-ABL1-targeted oral tyrosine kinase inhibitors (TKIs) into frontline chemotherapy regimens has been instrumental in improving the prognosis of patients with Ph + ALL [4–7]. However, combining intensive multi-agent chemotherapy with TKIs may lead to increased rates of infectious complications, organ toxicity, hospitalization, and mortality, particularly among adults with ALL age ≥60 years [8]. As a result, we and others have investigated novel chemotherapy-sparing approaches for patients with Ph + ALL.

As observed in patients with Ph-negative ALL, persistence of measurable residual disease (MRD, also known as minimal residual disease) following initial therapy for Ph + ALL, including induction with corticosteroids and TKI or chemotherapy in combination with TKI, is associated with increased risk of relapse. [6,9–11] Data regarding use of MRD to guide management of patients with Ph + ALL are less robust than those in patients with Ph-negative B-ALL. Early achievement of major molecular response (MMR, BCR-ABL1 transcript levels $< 10^{-3}$) stratifies patients with superior vs inferior disease-free survival, though timing of most prognostically valuable testing varies by study:

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achievement of MMR 3–4 weeks into treatment with TKI and corticosteroids [10] or TKI and chemotherapy [12], 2–3 months into treatment with TKI and chemotherapy [11,13], or during consolidation with TKI and chemotherapy [14] have all been reported to be favorable. Achievement of undetectable BCR-ABL1 transcripts (complete molecular response, CMR) following 3 months of dasatinib and initial prednisone additionally appears associated with lower incidence of relapse [10]. Attainment of CMR following 3 months of ponatinib and hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) similarly predicts superior overall survival among patients not proceeding to allogeneic hematopoietic cell transplantation (alloHCT) [9]. As such, kinetics of early MRD clearance (i.e. within the first 3 months of therapy) appear to predict durability of response to therapy. Emergence of MRD following alloHCT additionally predicts morphologic relapse [15].

The CD3/CD19-targeted bispecific T-cell engager blinatumomab (BLIN) has demonstrated single-agent activity in patients with B-ALL with MRD in first complete response (CR) or beyond, as well as in patients with relapsed/refectory (R/R) B-ALL, including R/R Ph + ALL. [16–20] However, there are minimal data and little exposition reflecting use of BLIN in combination with concurrent TKI therapy (BLIN + TKI) in patients with Ph + ALL to eradicate MRD or maintain MRD-negative CR in CR1 or beyond. Herein, we describe the observed safety and efficacy of BLIN + TKI in Ph + ALL as consolidative therapy for patients with minimal disease burden at our institution.

2. Materials and Methods

2.1. Study design

Institutional pharmacy records were queried to identify patients ≥18 years-old receiving BLIN at Memorial Sloan Kettering Cancer Center (MSKCC) between January 2011 and October 2018. Electronic medical records of BLIN recipients were reviewed, and patients with previously treated Ph + ALL in morphologic CR (MRD + or MRD-negative) who received BLIN concurrent with FDA-approved TKIs were identified (Fig. 1). The primary objectives of this retrospective study were to define the safety of BLIN + TKI and rates of achievement of MRD negativity by flow cytometry and/or quantitative real-time PCR (RT-qPCR) for BCR-ABL1 transcripts following BLIN + TKI consolidation. Secondary objectives included analysis of EFS and OS. This retrospective research protocol was approved by the Institutional Review Board (IRB) at MSKCC and all research was conducted according to the Declaration of Helsinki.

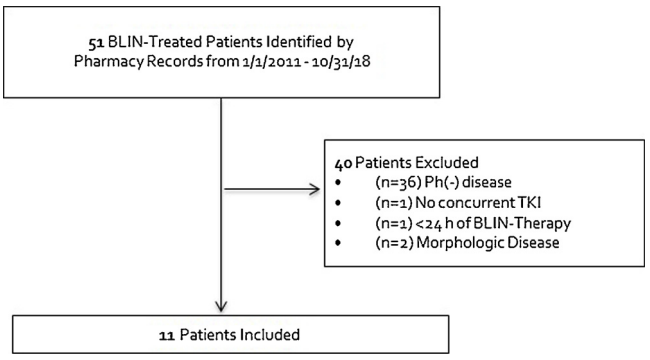

Fig. 1. Patient Inclusion. Identification of patients treated with concurrent blinatumomab (BLIN) and FDA-approved tyrosine kinase inhibitor (TKI) therapy for Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph + ALL) in morphologic complete response at Memorial Sloan Kettering Cancer Center.

2.2. Treatments

BLIN was administered per recommended dosing for adults ≥45 kg with relapsed/refractory B-ALL (conventional dosing), 9 mcg/day in the first week of cycle 1 with escalation to 28 mcg/day for 3 weeks, and subsequent dosing of 28 mcg/day for 4 weeks in successive 6-week cycles (n = 9) or per recently recommended dosing for adults ≥45 kg with MRD + B-ALL (MRD dosing), 28 mcg/day for 4 weeks repeated every 6 weeks (n = 2). One patient in the MRD dosing group transitioned to conventional dosing upon drug re-challenge due to initial intolerance of higher-dose BLIN. [16,17,21] TKIs were administered continuously, concomitant with BLIN, beginning on the first day of cycle 1. Ponatinib was started at a dose of 30 mg daily (n = 4) or 15 mg daily (n = 1); dasatinib was given at a dose of 140 mg daily (n = 2), 100 mg daily (n = 1) or 20 mg daily (n = 1), in the latter case to simulate an exposure of 100 mg daily in the setting of concomitant posaconazole; imatinib was started at 400 mg daily (n = 1); and nilotinib was administered at 400 mg twice daily (n = 1). MRD was assessed by FACS in addition to RT-qPCR for BCR-ABL1 transcripts in all patients following BLIN + TKI.

2.3. Assessment of response and toxicity

Morphologic CR was defined as the presence of < 5% blasts in the bone marrow (BM), absolute neutrophil count ≥1,000/μL, and platelets ≥100,000/μL in the peripheral blood with no documented extramedullary disease, similar to conventional response criteria for acute myeloid leukemia; CR with incomplete blood count recovery (CRi) was defined as a state meeting all criteria for CR except either residual neutropenia or thrombocytopenia. [22] MRD was assessed by 10-color multiparameter flow cytometry (FACS) and quantitative reverse transcription PCR (RT-qPCR) for BCR-ABL1 performed on BM aspirate samples. All RT-qPCR assays performed post-BLIN + TKI for patients in this series had sensitivity of < 0.004%. CMR was defined as CR without any detectable BCR-ABL1 transcripts by RT-qPCR in BM. Patients in CMR additionally had no detectable leukemic population by FACS in BM aspirate samples. Cytokine release syndrome (CRS) was graded per Lee et al. [23] Other toxicities, including neurologic toxicity, were graded per Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

2.4. Statistical considerations

EFS and OS were estimated using the Kaplan-Meier method. EFS was defined as time from initiation of BLIN + TKI (i.e. cycle 1 day 1 of BLIN) until date of morphologic relapse, confirmed refractory disease, or death in CR; patients not known to have any of these events are censored on the date of last follow-up. OS was defined as time from initiation of BLIN + TKI to death from any cause, with surviving patients censored at last follow-up. EFS/OS was not censored early at time of alloHCT. Duration of CMR was calculated as time from first confirmation of CMR by BM biopsy until time of morphologic or molecular relapse. Time-dependent variables were compared within groups using log-rank tests.

3. Results

3.1. Demographic and clinical characteristics

Thirteen patients were treated with BLIN + TKI for Ph + ALL (Fig. 1). Two patients with overt morphologic relapse receiving BLIN + TKI were excluded from this analysis. Of the remaining 11 patients, six were male (54%) with a median age of 61.2 years (range, 27–72.1) at time of BLIN + TKI initiation (Table 1**)**. Nine pts had detectable MRD after initial therapy (81%) in CR1 (n = 7; CRi in 1 patient), or CR2 (n = 2); two patients had undetectable BCR-ABL1

Table 1
Patient characteristics and clinical outcomes.

Pt #	Extent of ALL at start of BLIN + TKI			Age at BLIN + TKI	Sex	Disease Status	Relapse Post-AlloHCT	BCR-ABL1 Transcript	Baseline ABL Mut	Partner TKI	Trans-aminitis	CRS	Best Response	Cycles to CMR	Total Cycles	F/U (mo)	Clinical Status at Last F/U
	Disease Burden	FACS	PCR														
1	Detectable MRD by BCR-ABL1 PCR +/- FACS	0.061%	0.232%	55.4	F	CR2	Y	p190	N	PON	Y	N	CMR	1	5	20.0	Alive on PON Maint
2		1.000%	0.005%	46.9	F	CR2	Y	p190	Q252H	PON	Y	Y	CMR	1	2	11.6	Alive post- 2nd AlloHCT after CMR
3		0.001%	0.126%	68.0	F	CR1	N	p210	N	DAS	Y	N	CMR	2	4	18.4	Alive on PON Maint
4		0.036%	1.713%	72.1	F	CR1	N	p190	T315I, 35 nt ins	PON	N	N	MRD – (FACS); BCR-ABL1 PCR +	N/A	3	9.4	Died in CR from complications post-AlloHCT
5		0.013%	0.072%	61.2	M	CR1	N	p190	35 nt ins	PON	Y	N	CMR	1	1	10.0	Alive post- AlloHCT after CMR
6		0.002%	0.019%	51.2	F	CR1	N	p190	35 nt ins	NIL	N	N	CMR	1	3	9.4	Alive on NIL Maint
7		0.000%	0.020%	58.5	F	CR1	N	p210	N	DAS > PON > DAS	N	N	CMR	1	4	7.3	Alive on DAS Maint
8		0.039%	0.045%	62.0	F	CR1	N	p190	N	IMA > NIL	Y	Y	CMR	1	1	4.6	Alive post AlloHCT after CMR
9		0.120%	1.170%	64.0	M	CR1	N	p190	T315I, 35 nt ins	PON	Y	Y	CMR	1	3	3.4	Alive on cont. BLIN + PON
10	No Measurable ALL			27.7	M	CR2	Y	p190	N	DAS	N	N	Maint. CMR	N/A	5	18.7	Alive on DAS Maint
11				65.4	M	CR1	N	p190	N	DAS	N	N	Maint. CMR	N/A	4	15.3	Alive on DAS + POMP Maint

Legend: Pt = patient; F = female; M = male; 35 nt ins = 35-nucleotide insertion detected between exon 8 and exon 9 of ABL gene; POMP = 6-mercaptopurine, vincristine, methotrexate, prednisone; ABL Mut = ABL Kinase Mutations; AlloHCT = allogeneic hematopoietic cell transplantation; Maint = maintenance; CMR = complete molecular response; F/U = follow-up; mo = months; MRD = minimal residual disease; CR = complete response; TKI = tyrosine Kinase Inhibitor; IMA = imatinib; PON = ponatinib; DAS = dasatinib; NIL = nilotinib; FACS = fluorescence activated cell sorting (flow cytometry); N/A = not applicable.

transcripts in CR1 (n = 1) or CR2 (n = 1) at the time of BLIN + TKI treatment. Median prior lines of treatment were 1 (range, 1–5, see Supplementary Table 1), and 3 patients had undergone prior alloHCT (see Supplementary Table 2). ABL1 kinase domain mutations were present in 5 patients (45%): T3151 + 35 nucleotide insertion (n = 2), 35 nucleotide insertion (n = 2), and Q252H (n = 1). Initial companion TKIs were used in the following manner: ponatinib (n = 5), dasatinib (n = 4), nilotinib (n = 1) and imatinib (n = 1). Ponatinib was chosen in the setting of T315I mutations (n = 2) or in patients with progression/inadequate response following one or more second-generation TKIs (n = 3). These initial companion TKIs represented the first (n = 3), second (n = 5), or fourth (n = 3) TKIs used by each individual. Initial companion TKIs were continued from the immediate prior line of therapy or were changed following inadequate response to prior therapy and administered as monotherapy prior to introduction of BLIN (Supplementary Table 1). Of the three patients whose initial TKI represented the BLIN companion TKI, two had received dasatinib combined with ruxolitinib and dexamethasone on clinical trial (one had MRD); one transitioned from dasatinib and hyper-CVAD following severe nephrotoxicity associated with methotrexate (and had MRD). Median duration of therapy prior to initiation of BLIN was 3.5 months (range, 3.0–5.5 months) in these three patients. None of the 3 patients who had relapsed post-alloHCT had received maintenance TKI, though two received TKI for molecular relapse preceding morphologic relapse, and all received TKI-based therapy (range, 3.0–13.9 months) prior to receiving BLIN + TKI (Supplementary Table 2). No patients had active central nervous system (CNS) disease at the time of BLIN + TKI initiation; patients received intrathecal (IT) chemotherapy as CNS prophylaxis during the 2-week period off BLIN between cycles (n = 9) or received IT chemotherapy prophylaxis prior to BLIN (n = 2); no patients received IT chemotherapy during BLIN infusion. Patients completed a median of three cycles of BLIN + TKI (range, 1–5).

3.2. Efficacy

Patients with MRD prior to initiation of BLIN + TKI were considered evaluable for response. Among the 9 patients in MRD + CR when beginning BLIN + TKI consolidation, 8 (88%) achieved CMR after a median of one cycle (range, 1–2). While the patients without measurable Ph + ALL prior to BLIN + TKI consolidation are not evaluable for response, both maintained CMR. Median duration of follow-up among survivors was 10.8 months (range, 3.5–20.0); ten patients (91%) are in ongoing response. None of the responding patients have subsequently relapsed; three (27%) patients underwent subsequent alloHCT in CMR and remain alive in ongoing CMR (Fig. 2A). One-year EFS among all patients is 90%. Only one patient in the cohort died; she achieved undetectable Ph + ALL by FACS but did not attain CMR after three cycles of BLIN + TKI and developed of morphologic relapse within 4 months of beginning BLIN + TKI. She achieved CR2 after two cycles of single-agent inotuzumab ozogamicin, but subsequently died in CR of alloHCT-related complications. All remaining patients (n = 10) are alive in continued response at last follow up; the median EFS and OS were not reached (Fig. 2A&B). Seven of 11 patients did not undergo alloHCT following BLIN + TKI consolidation, and 7/7 remain alive in CMR as of last assessment at median 15.3 months of follow-up (range, 3.5–20.0 months); two of these seven patients received BLIN + TKI for relapse following a first alloHCT but did not undergo second alloHCT post-BLIN + TKI.

3.3. Safety

The combination of BLIN + TKI was generally well tolerated. CRS occurred in three MRD + patients, with two grade 1 events in BLIN + ponatinib recipients and one grade 2 event in the BLIN + imatinib recipient, all during cycle 1 (Fig. 3A). Grade 1 events resolved with temporary cessation of BLIN and a re-challenge within

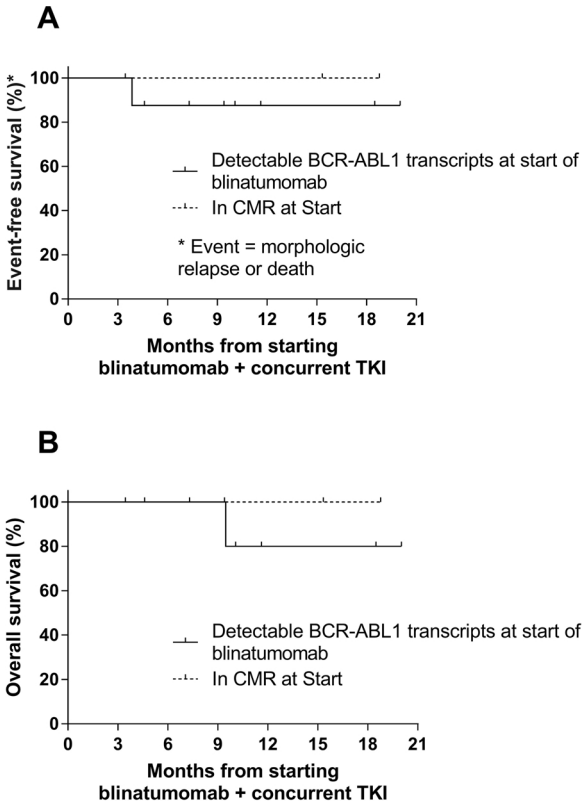

Fig. 2. Survival outcomes. (A) Event-free survival (EFS) and (B) overall survival among patients treated with concurrent blinatumomab and tyrosine kinase inhibitor therapy (TKI) for Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph + ALL) in morphologic complete response, stratified by patients with detectable Ph + ALL by BCR-ABL1 transcripts ± flow cytometry (solid lines) or in complete molecular response (CMR) at initiation of concurrent blinatumomab + TKI therapy (dashed lines).

hours. The grade 2 event occurred in a 45-kilogram (kg) patient with residual MRD who began BLIN at 28 mcg/day in combination with imatinib. Upon single-agent BLIN re-challenge after infusion cessation, the patient experienced resurgence of grade 2 CRS in addition to grade 1 neurotoxicity. The patient was observed off therapy for six days and successfully re-challenged on single-agent BLIN (9 mcg/day) with titration to 20 mcg/day (15 mcg/kg/day) on day 8 of re-challenge as weight trended to under 45 kg. She tolerated her remaining BLIN therapy with no further complications; companion TKI was changed to nilotinib secondary to patient preference. Grade 1 neurotoxicity (transient dysarthria) was observed in a BLIN + ponatinib recipient who had experienced grade 1 CRS, resolving after temporary cessation of BLIN and subsequent re-challenge within hours. No patients received tocilizumab or dexamethasone for management of CRS or neurotoxicity.

Transaminitis occurred in 6/11 patients (55%), including 4/5 BLIN + ponatinib recipients; all events were grade 2 (Fig. 3B). Transaminitis resolved without cessation of BLIN in all patients; no patient warranted cessation of BLIN secondary to transaminitis. Ponatinib was dose attenuated from 30 mg to 15 mg daily in two patients shortly into the course of BLIN + ponatinib therapy to prevent worsening transaminitis, on cycle 1 day 4 in one patient and cycle 1 day 6 in the other. No further dose adjustments of ponatinib were required and transaminitis resolved without subsequent intervention or sequelae in these patients.

4. Discussion

Eradication of residual MRD following conventional induction and consolidation therapy has historically been a challenge in the

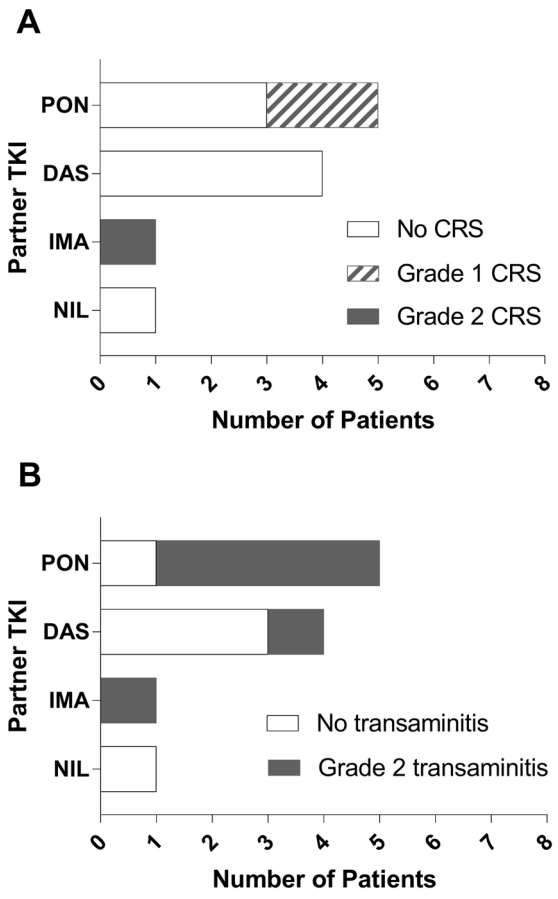

Fig. 3. Severity of major toxicities. Toxicities experienced during cycle 1 of concurrent blinatumomab and tyrosine kinase inhibitor (TKI) therapy, stratified by companion TKI, including (A) cytokine release syndrome (CRS) and (B) transaminitis. PON = ponatinib, DAS = dasatinib, IMA = imatinib, NIL = nilotinib.

management of B-ALL [24,25]. Among patients with Ph-negative B-ALL and persistent MRD, eradication of MRD using BLIN has been associated with significantly longer relapse-free survival and OS compared to MRD non-responders [17,19]. The durable remissions observed following BLIN consolidation for MRD-positive Ph-negative ALL comport with observations from several studies suggesting patients with low disease burden at the time of BLIN initiation derive optimal benefit, compared with those with higher leukemic burden [16,17,25,26]. Our small, retrospective series suggests BLIN + TKI may be a safe and effective consolidation strategy for patients with Ph + ALL and detectable MRD to achieve CMR. While the two patients in CMR at time of BLIN + TKI initiation are not evaluable for efficacy, BLIN + TKI may be a feasible strategy to sustain CMR in selected patients, though a larger study with more extended follow-up would be required. Most MRD + patients (88%) attained CMR after a median of one cycle and continue to exhibit no evidence of disease; all responders, including those who received alloHCT after successful BLIN + TKI therapy (n = 3), were alive at last follow up.

Efficacy observed in this very small series suggests BLIN + TKI (vs. BLIN monotherapy or TKI monotherapy) may optimize response in patients with Ph + ALL. A single-arm phase II study in adults with B-ALL with persistent MRD or MRD relapse in morphologic CR1 or beyond demonstrated an 80% rate of MRD response with BLIN monotherapy overall; nearly all responses occurred within the first cycle. Among Ph + patients included in their analysis, 3/5 (60%) achieved MRD-negativity. We observed efficacy similar to another single-center report examining BLIN + TKI in Ph + leukemias in molecular or morphologic relapse. In that study, all four patients with Ph + B-ALL in molecular relapse treated with BLIN + TKI attained negative MRD status by FACS and RT-qPCR, but within a median of two cycles (range, 1–3), in contrast to a median of one cycle in our population. Of note, assessment of rates of CMR among patients with MRD was not the primary objective of their study [20]. It remains unlikely, albeit possible, that the durable molecular remissions observed herein can be attributed to TKI therapy alone. While a small subgroup of patients treated with dasatinib and corticosteroids achieve CMR after 3 months of therapy (15% in the series by Foa et al.) [10], those who do not tend to have an inferior prognosis. Among previously-treated patients with Ph + ALL, responses to dasatinib [27,28] or ponatinib [29,30] monotherapy, when observed, appear poorly durable (median duration of hematologic/cytogenetic response of 3–5 months) and rates of hematologic response to nilotinib [31] or bosutinib [32] monotherapy are disappointing.

Most adverse events leading to treatment interruptions resolved rapidly after stopping BLIN. No grade ≥2 neurologic events or grade ≥3 CRS were observed. CRS was observed at a similar rate to the previously published experience with combination BLIN + TKI, [20] but appeared significantly milder; only one grade 2 event occurred in cycle 1. Incidence and severity of neurologic toxicity was less than that of other studies of BLIN or BLIN + TKI, with only two documented grade 1 events [16–18,20]. In another study of BLIN + TKI, grade 3 seizures were noted in 2 patients with Ph + ALL and MRD [20]. While it remains uncertain whether CNS involvement by B-ALL increases risk of severe neurologic toxicity in BLIN recipients, no patients in this cohort had active CNS disease whereas 3 of 3 patients with CNS disease in another series experienced neurologic toxicity during BLIN + TKI therapy, including seizures/status epilepticus in 2 patients [20]. Assessment of BLIN toxicity in a larger cohort of patients with CNS involvement could characterize the associated risks of neurologic toxicity more definitively. In patients for whom TKI is changed with plans to add BLIN shortly thereafter, the optimal duration of TKI monotherapy is unclear, though a brief period of monotherapy as employed herein (median 1 month, Supplementary Table 1) may help to assess early toxicities and avoid diagnostic uncertainty in the setting of overlapping toxicities of BLIN.

To our knowledge, this report is the first to detail the incidence and severity of transaminitis associated with BLIN + TKI. In a phase II clinical trial of BLIN monotherapy in R/R Ph + ALL, transaminase elevations were reported in 13% of patients, with a 4% incidence of grade 4 elevations. Transaminitis was observed at higher frequency in our small cohort with (6/11 patients, 54%) but no occurrences were grade > 2. All cases were self-limited. Patients treated with BLIN + ponatinib exhibited the highest incidence of transaminitis. Independently, transaminase elevations have been reported to occur in approximately 41% of patients treated with ponatinib monotherapy, suggesting the small, incremental risk of combination therapy may be outweighed by the efficacy benefit of combination BLIN + ponatinib [33]. Dose reduction of PON to 15 mg daily was well tolerated in all re-challenged patients, with no reported recurrence of transaminitis or loss of response. Optimal dosing of companion TKIs, particularly BLIN + ponatinib, warrants further exploration to limit incidence of transaminitis.

Selection of companion TKI likely has implications for toxicity, as noted above, as well as for anti-leukemic activity. As a clear example, dasatinib inhibits Src family kinases (SFKs), which contribute to signaling downstream of the T-cell receptor and ultimately support T-cell activation [34–37], and its immunosuppressive effects have been described *in vitro* and *in vivo* [37,38]. These observations, as well as *in vitro* studies suggesting dasatinib and ponatinib may impair T-cell proliferation and cytokine production in the setting of BLIN, highlight the potential implications of off-target kinase inhibition on the activity of immunotherapy [39]. However, in clinical use, the implications of dasatinib on T-cells appear more complex, with lymphocytosis and clonal expansion of cytotoxic T-cells observed in a significant subgroup of

patients and associated with better response [40]. Dasatinib may have greater activity against regulatory T-cells and $CD4^+$ T-cell subsets (vs against cytotoxic T-cells responsible for BLIN-facilitated activity) [37,41]. Additionally, dasatinib may increase the proportions of granzyme B-expressing T-cells and effector memory T-cells [42]; BLIN is also associated with expansion in effector memory T-cells [43]. This small series suggests dasatinib and ponatinib do not abrogate BLIN activity, but evaluation of a larger number of patients would be required to characterize efficacy more robustly. The optimal companion TKI, if any, remains uncertain. Correlative studies aimed at assessing T-cell expansion and phenotype *in vivo*, including markers of T-cell exhaustion, during BLIN + TKI therapy may further clarify the immunomodulatory effects of each companion TKI.

In contrast to most currently available literature investigating BLIN and BLIN + TKI, all patients in our study had Ph + ALL with minimal to undetectable disease burden. Nevertheless, interpretation of our results are limited by small cohort size, heterogeneity of companion TKI selection, BLIN dosing, and post-BLIN therapy, and retrospective data extraction from a single center. Longer follow-up and prospective study is warranted to corroborate our observations. However, the incorporation of BLIN + TKI into treatment paradigms for Ph + ALL may optimize response with minimal incremental toxicity, and treatment with BLIN in CR1 with persistent MRD may be beneficial. Of note, early administration of BLIN in CR1 may additionally suppress resistant clones with single or compound mutations in ABL kinase and may facilitate successful chemotherapy-free treatment of Ph + ALL by deepening and extending response. Such an approach may be particularly attractive in older adults or those with comorbidities, for whom the toxicity profile of BLIN + TKI may be favorable (vs chemotherapy + TKI). BLIN + TKI may serve as a bridge to first or subsequent alloHCT, as effective definitive consolidative therapy in patients not proceeding to alloHCT, or as treatment for molecular relapse post-alloHCT. Further investigation of this strategy is ongoing and may represent a safe and effective consolidative option for adults with Ph + ALL in morphologic CR.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.leukres.2019.02.009.

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