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Combining Blinatumomab with Targeted Therapy for BCR-ABL Mutant Relapsed/ Refractory Acute Lymphoblastic leukemia

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Keywords

Bcr-abl tyrosine kinase inhibitors; Philadelphia chromosome positive; acute lymphoblastic leukemia; Blinatumomab

Acute lymphoblastic leukemia (ALL) carries a poor prognosis in adults with a 5 year survival of only 25 – 40% [1]. With current induction chemotherapy approaches, about 90% of adult patients will achieve CR, but despite this early success, most will relapse and have significantly shorter survival despite salvage chemotherapy and allogeneic hematopoietic stem cell transplantation (HCT) [2–4]. Due to these unsatisfactory outcomes, there is a substantial need to develop new treatment strategies for patients with relapsed or refractory B-cell ALL. About one quarter of adult patients with ALL are positive for Philadelphia chromosome (Ph), and its presence in ALL was historically associated with worse outcomes [5–7]. Blinatumomab, a bispecific antibody against CD19 and CD3, gained accelerated FDA approval in 2014 for the treatment of relapsed or refractory, Ph⁻ B-cell ALL based on the results of a phase II trial [8]. This study specifically excluded patients with Ph⁺ disease as they preferentially receive salvage treatments in combination with BCR-ABL tyrosine kinase inhibitors. We have been using blinatumomab at our institution for patients with relapsed/refractory B-cell ALL since its approval and have extended its use to Ph⁺ disease. There are several ongoing prospective trials evaluating the efficacy of TKIs when combined with blinatumomab, however, there is paucity of published data on this combination. Here we present our experience using blinatumomab concurrently with TKIs for patients with relapsed/ refractory Ph⁺ B-cell ALL.

We conducted a retrospective chart review of all 5 adult patients who received blinatumomab while on TKIs between January 2015 and August 2017 at Roswell Park Cancer Institute. Inclusion criteria were diagnosis of Ph⁺ B-cell ALL that is primary refractory or relapsed after standard first-line therapy, treatment with 1st, 2nd or 3rd generation TKIs and exposure to blinatumomab while on TKI therapy. We also included a sixth patient who received blinatumomab as single agent followed by TKI for relapsed disease. Baseline characteristics,

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treatment-related adverse events and outcomes including response, relapse and overall survival were analyzed and herein reported.

Baseline patient characteristics are summarized in Table 1. Median age was 65 years (range 23 – 83). Three patients had relapsed and three had refractory disease after first-line induction chemotherapy; one of the patients (Pt. # 6) relapsed after autologous HCT. Two patients were diagnosed with leukemic infiltration of the CNS and received IT chemotherapy. All patients had previous exposure to dasatinib, and two patients received ponatinib. All patients had detectable disease by one or more assays (BCR-ABL1 p190 molecular testing, morphological disease relapse or MRD positivity as determined by flow cytometry) in the bone marrow before the start of blinatumomab. All patients received IV blinatumomab salvage therapy per standard guidelines (9 mcg daily on days 1–7 followed by 28 mcg daily on days 8–28 in a 6 weeks cycle). None of the patients received blinatumomab as part of a clinical trial. At the time of the institution of salvage therapy, 3 patients had morphological leukemia in the bone marrow and 3 had evidence of residual disease detectable by molecular and flow cytometric techniques. The median time from diagnosis to the start of blinatumomab therapy was 8 months (Range: 3 – 46 months). Patients received an average of 2 cycles (range: 0.5 – 4) of blinatumomab. Three patients were switched from dasatinib to ponatinib due to disease progression but tyrosine kinase domain mutation testing was not performed. After a median follow up of 12 months (range: 2 – 17 months) from initiation of blinatumomab and TKI therapy, all six patients are alive. One patient was primarily refractory to blinatumomab and was taken off the drug due to worsening peripheral blood blasts count after 15 days of treatment, but it is notable that she was receiving single agent blinatumomab at that time without resumption of her TKI. This patient subsequently received salvage chemotherapy in combination with a TKI and has achieved an excellent response with ongoing molecular CR. Three of five other patients achieved complete molecular remission (CMR) following combination therapy with blinatumomab and a TKI, one patient attained major molecular remission (MMR) while one patient is in complete cytogenetic remission (CCR) after two cycles of blinatumomab/TKI with decreasing p190 levels in bone marrow. One out of three patients who achieved CMR has had an MRD relapse with detectable p190 levels. The average number of cycles to best response with blinatumomab was 1.6. Outcomes with combination therapy are summarized in Table 2. In our experience, this combination was well tolerated. None of the patients received any steroids while on combination therapy except as premedication for blinatumomab. Although some patients had adverse events while on treatment it is difficult to distinguish completely whether these arose from the blinatumomab or from the TKI. One patient (Pt. # 6) developed hypertensive urgency while receiving blinatumomab resulting in an interruption of therapy for 3 days. One patient developed severe neutropenia and thrombocytopenia while on blinatumomab and TKI, and required G-CSF administration for support of her counts. The cytopenias appear to be attributable to the concomitant treatment with dasatinib, as they persisted after completion of blinatumomab and have since responded to dose-reduction of the dasatinib. Two patients had severe infections while on treatment requiring hospitalization. Neither cytokine release syndrome nor neurotoxicity were observed in any of the patients. Other adverse effects during treatment are listed in Table 2.

Our results in five adult patients who received the combination of blinatumomab with a TKI as salvage treatment for Ph⁺ relapsed or refractory B-ALL, and in one patient who received sequential therapy, suggest that this combination overall is safe and well tolerated. Although all of our patients had favorable outcomes, the number of patients in this study is small. Due to activation of T-cells by blinatumomab, CRS is a concern, especially during the first cycle of treatment [9]. Interestingly, none of our patients had evidence of CRS or neurotoxicity which could be related to a lower level of disease burden in these patients who were concurrently receiving TKI therapy and some of whom only had MRD+ disease. All five patients who had disease progression on prior TKI therapy +/- cytotoxic chemotherapy regimens demonstrated evidence of clinical activity following combination blinatumomab and TKI therapy pointing towards possible additive or synergistic anti-tumor activity with these combined biological agents. Recently, Martinelli and colleagues reported the results of a phase II trial of blinatumomab treatment for relapsed or refractory Ph+ ALL involving 45 patients who had failed prior therapy with second generation or later TKI [10]. Sixteen patients (36%) achieved CR/CRh during the first 2 cycles with OS of 7.1 months. The median age of that cohort was 55 years and patients were treated with blinatumomab as single agent. The results of this trial led to FDA approval of blinatumomab for relapsed or refractory Ph⁺ ALL in July 2017. Among our patients, the only patient who did not have a favorable response to blinatumomab received single-agent therapy, which may be indicative of a potential benefit with combination therapy. The majority of our patients were older (4 of 5, median age 66 years) and all tolerated this regimen well with limited complications, even the 1 patient over 80 years old, suggesting that this regimen may be a particularly attractive option for those individuals whose comorbidities and/or age render them ineligible for intensive salvage chemotherapy regimens, CAR-T cells or allogeneic stem cell transplantation. Considering the very poor prognosis for older patients with relapsed/refractory B-ALL using these other approaches (salvage chemotherapy and allogeneic HCT) the fact that all five patients are alive and well over a year since initiating this regimen is clinically meaningful, particularly in the absence of allo-HCT in 4 patients. Similar results are recently reported by Assi et al. in a case series of 9 patients with relapsed/ refractory Ph⁺ ALL and 3 patients in CML blast crisis treated with combination of blinatumomab and TKI [11]. Further studies involving larger numbers of patients and prospective analysis are required to validate the magnitude of benefit with this approach. There are two prospective clinical trials (NCT02744768, NCT02143414) in the initial stages of analyzing this combination and their results are eagerly awaited.

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References:

1. Rowe JM, Buck G, Burnett AK, et al. Induction therapy for adults with acute lymphoblastic leukemia: Results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. *Blood*. 2005;106(12):3760–3767. [PubMed: 16105981]
2. Kantarjian HM, Thomas D, Ravandi F, et al. Defining the course and prognosis of adults with acute lymphocytic leukemia in first salvage after induction failure or short first remission duration. *Cancer*. 2010;116(24):5568–5574. [PubMed: 20737576]
3. Fielding AK, Richards SM, Chopra R, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. *Blood*. 2007;109(3):944–950. [PubMed: 17032921]
4. Oriol A, Vives S, Hernandez-Rivas JM, et al. Outcome after relapse of acute lymphoblastic leukemia in adult patients included in four consecutive risk-adapted trials by the PETHEMA study group. *Haematologica*. 2010;95(4):589–596. [PubMed: 20145276]
5. Pullarkat V, Slovak ML, Kopecky KJ, Forman SJ, Appelbaum FR. Impact of cytogenetics on the outcome of adult acute lymphoblastic leukemia: Results of southwest oncology group 9400 study. *Blood*. 2008;111(5):2563–2572. [PubMed: 18156492]
6. Ottmann OG, Wassmann B. Treatment of philadelphia chromosome-positive acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program*. 2005:118–122. [PubMed: 16304368]
7. Thomas X, Boiron JM, Huguet F, et al. Outcome of treatment in adults with acute lymphoblastic leukemia: Analysis of the LALA-94 trial. *J Clin Oncol*. 2004;22(20):4075–4086. [PubMed: 15353542]
8. Topp MS, Gokbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: A multicentre, single-arm, phase 2 study. *Lancet Oncol*. 2015;16(1):57–66. [PubMed: 25524800]
9. Teachey DT, Rheingold SR, Maude SL, et al. Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. *Blood*. 2013;121(26):5154–5157. [PubMed: 23678006]
10. Martinelli G, Boissel N, Chevallier P et al. Complete Hematologic and Molecular Response in Adult Patients With Relapsed/Refractory Philadelphia Chromosome-Positive B-Precursor Acute Lymphoblastic Leukemia Following Treatment With Blinatumomab: Results From a Phase II, Single-Arm, Multicenter Study. *Journal of Clinical Oncology*. 2017;JCO.2016.69.353.
11. Assi R, Kantarjian H, Short NJ, et al. Safety and efficacy of blinatumomab in combination with a tyrosine kinase inhibitor for the treatment of relapsed philadelphia chromosome-positive leukemia. *Clin Lymphoma Myeloma Leuk*. 2017 doi: S2152-2650(17)30840–6
12. Kantarjian H, Thomas D, O'Brien S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. *Cancer*. 2004;101(12):2788–2801 [PubMed: 15481055]

Table 1 –

Baseline Characteristics and Initial Therapy for All Patients

Pt.	Sex (Age, y)	Cytogenetics*	CNS Disease	Induction Chemotherapy	Steroids with Induction	Lines of Rx	Initial TKI
1	F (82)	Complex	Yes	Per CALGB 10701 [‡]	Yes	1	Dasatinib
2	M (64)	Complex	No	Per CALGB 10701 [‡] with Rituximab	Yes	1	Dasatinib
3	F (23)	Normal	Yes	HyperCVAD ¹² with Dasatinib and Rituximab	Yes	1	Dasatinib
4	F (68)	Normal	No	POMP [‡]	Yes	2	Dasatinib
5	F (43)	Complex	No	HyperCVAD ¹² with Dasatinib	Yes	1	Dasatinib
6	F (66)	Normal	No	Per CALGB 10701 [‡]	Yes	2	Dasatinib

* Other than t(9;22). Details as follows:

Patient 1: 46,X,?(X;10)(q24;q26),dic(7;12)(p12;p11.2),t(9;22)(q34;q11.2),i(17)(q10),+mar {33}

Patient 2: 43-44,XY,add(3)(p12),?der(7)t(7;14)(p12;q11.2),-8,-9,t(9;22)(q34;q11.2),-13,-14,?add(19)(p13.1),+der(22)t(9;22)(q34;q11.2),+mar{12}{20}

Patient 5: 46,XX,t(9;22)(q34;q11.2),add(19)(p13.2),del(20)(?q11.2?)(q14),46,XX,t(9;22)(q34;q11.2){1},46,XX{9}

[‡]CALGB 10701: NCT01256398 - consisting of courses I/IIA of induction consisting of dasatinib 140mg orally days 1-37 + dexamethasone 10mg/m2 days 1-7 and 16-21; CNS prophylaxis with IT methotrexate 15mg on day 15; followed by 1 year of maintenance chemotherapy consisting of: dasatinib 100mg orally daily + 6-mercaptopurine (6MP) 60mg/m2 orally at bedtime + methotrexate (MTX) 20mg/m2 orally weekly + vincristine (VCR; 2mg cap) 1.4mg/m2 IV q4wks+ dexamethasone 10mg/m2 5 days every 4 weeks followed by single agent dasatinib 100mg orally daily

[‡]POMP regimen: Prednisone, Vincristine, Methotrexate and 6-Mercaptopurine

Table 2 –
Disease Assessment in Bone Marrow Before and After Blinatumomab Treatment with Toxicities

Pt.	TKI used with Blin	Pre-Treatment Disease Assessment			Post-Treatment Disease Assessment [*]		No. Cycles	Best Response	Time to best Response (Months)	Allo-HCT	Toxicities (grade3)
		Bone Marrow Blasts (%)	Bone Marrow MRD Value ^{***} (%)	p190 levels (%)	Bone Marrow MRD Status ^{***} (%)	p190 levels (%)					
1	Dasatinib	67	Not Available	119.47	Negative	Undetectable	4	CMR	1	No	Neutropenia, Thrombocytopenia, Cellulitis with bacteremia
2	Ponatinib	2	0.20	0.017	Negative	0.0056%	2	MMR	2	No	Hypertension, Hyperglycemia
3	Dasatinib	1	0.7	0.19	Negative	Undetectable	2	CMR	2	Yes	C. diff colitis, Pneumonia
4	Ponatinib	46	40	283.5	Negative	Undetectable	4	CMR	1	No	None
5	Dasatinib	3	Negative	0.5	Negative	0.087	2 [†]	CCR	2	No	None
6	Ponatinib	62	Not Available	180.04	Not Available	Not Available	0.5	Progression [‡]	N/A	No	Hypertensive urgency

^{*} All patients were continued on a TKI after completion of blinatumomab

^{***} Based on COG MRD Flow cytometry analysis including markers against CD19, CD45, CD20, CD10, CD38, CD58, CD34, CD9, CD13, CD33, CD71, AND SYTO16

[†] Ongoing treatment

[‡] Diagnosed on worsening peripheral blood blast count

Abbreviations: MRD–Minimal Residual Disease, CMR–Complete Molecular Remission, MMR–Major Molecular Remission, CCR–Complete Cytogenetic Remission, HCT–Hemamiddleleiotic Cell Transplantation