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Blinatumomab and ponatinib with central nervous system treatment intensification for adolescents and young adults with Philadelphia-positive B-cell acute lymphoblastic leukemia

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Philadelphia chromosome-positive B-cell acute lymphoblastic leukemia (Ph+ B-ALL) accounts for up to 20% of Adolescents and Young Adults (AYAs) with acute lymphoblastic leukemia.(1) Earlier data suggested that early complete molecular response (CMR) is a strong prognostic marker in patients treated with chemotherapy and TKI, suggesting a favorable outcome that may obviate the need for stem cell transplantation.(2-6) However, this was observed in a cohort of older patients, in whom non-relapse mortality (NRM) was higher than in the AYA patients; hence, the generalizability to the AYA patient population was limited.

More recently, several prospective studies have evaluated a blinatumomab-TKI-based approach using dasatinib or ponatinib for newly diagnosed Ph+ B-ALL, with SCT offered only to a select few patients.(7-11) The median age across those studies was above 50 years, and data on the AYA patient population were limited. Using this approach, central nervous system (CNS) relapse appears to be an emerging issue. In those studies, the role of early CMR is poorly established. In the report by Short *et al*., the BCR::ABL1 transcript type and early CMR did not significantly impact the risk of relapse.(12) In univariate analysis of those patients, white blood cell (WBC) count ≥ 70 $\times 10^3/\mu L$ at diagnosis, baseline CNS involvement, and *VPREB1* deletion were significant predictors of relapse. In multivariate analysis, only high WBC retained prognostic significance.(12) In the extended follow-up of the D-ALBA study, patients with the *IKZF1*$^{-plus}$ molecular signature treated with dasatinib-blinatumomab had worse outcomes. Early CMR was a significant predictor after dasatinib induction, but lost significance after two cycles of blinatumomab.(7) It is possible that, due to CML-like biology in some Ph+ B-ALL and treatment-resistant kinases, the role of early CMR in blinatumomab-based treatment may not be a strong predictor, as observed with chemotherapy-based approaches. Therefore, transplant decisions will likely need to be further refined based on additional prognostic factors.

In this report, we examined our AYA patients treated with blinatumomab and ponatinib with CNS treatment intensification for high-risk patients, and compared them with our previously reported historical AYA-specific transplant data.(13) In this multicenter observational study (King Faisal Specialist Hospital and Research Center (KFSH&RC),

Riyadh, Saudi Arabia, and King Fahad Medical City (KFMC), Riyadh, Saudi Arabia). We included all newly diagnosed AYA patients (aged 14-45 years) who were treatment naïve or had received 2 or fewer cycles of chemotherapy before referral to the treating centers and were started on blinatumomab with ponatinib. Generally, patients received a pre-phase with ponatinib with steroids, followed by 5 cycles of blinatumomab and ponatinib, with 16-17 intrathecal chemotherapy alternating between methotrexate 12mg and cytarabine 100mg. Patients with positive CNS disease or considered at high risk for CNS disease (presenting WBC ≥50 $\times 10^3/\mu L$, extensive extramedullary disease) received one cycle of CNS-directed systemic chemotherapy (Methotrexate 1000mg/m² IV on Day 1 and cytarabine 3 g/m² IV every 12 hours for four doses on Days 2-3, with Intrathecal cytarabine on Day 2 and Methotrexate on Day 8) at the end of blinatumomab cycles. The starting dose of ponatinib was 45mg for patients with a Framingham risk score <10%. Prophylaxis with apixaban 2.5mg PO BID was administered during high-dose ponatinib (45/30mg) once the platelet count was more than 70. The dose of ponatinib was reduced to 30mg during consolidation (usually consolidation 3) if patients achieved MRD negativity by flow cytometry, and to 15mg only at the end of blinatumomab cycles.

In this analysis, CMR was defined as two consecutive readings with a BCR::ABL1 transcript of less than 0.01% using local qPCR. Morphologic relapse is defined by 5% or more lymphoblasts or evidence of extramedullary disease. Molecular relapse was defined as a one- or more-log increase in BCR::ABL1 transcripts by qPCR. RFS was defined as the time from remission to relapse or death. Cytokine release syndrome (CRS), and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded according to the 2019 ASTCT consensus criteria. Adverse events were graded according to NCI-CTCAE v5.0 criteria. The Kaplan-Meier method was used to estimate OS and RFS probabilities, and the reverse Kaplan-Meier method was used to estimate the median follow-up. All statistical analyses were performed using GraphPad Prism (GraphPad Software, San Diego, CA, USA). This study was conducted in accordance with ethical standards and received approval from the Institutional Review Board (IRB) at King Faisal Specialist Hospital and Research Center (KFSHRC) and King Fahad Medical City (KFMC).

A total of 12 patients were included, with a median age of 28.1 years (16.2-45.2 years), and the majority were male (Table). A high presenting WBC (≥30 $\times 10^3$/μL) was noted in the majority of patients (67%). Additional cytogenetic abnormalities were noted in 44% of patients, and the most common BCR::ABL1 transcript was p190 in 63% of patients. Hepatosplenomegaly by imaging was noted in 4 patients (33%). Of the 7 patients with diagnostic samples available before receiving any chemotherapy or steroids, 6 patients had positive myeloid markers at diagnosis (the majority are CD13 and/or CD33). Four patients were enrolled in the protocol while in remission after receiving chemotherapy before referral, and all remaining patients achieved complete remission with induction. After the first cycle of blinatumomab and ponatinib, the rate of MRD negativity by qPCR for BCR::ABL1 was 50%. All patients but one achieved MRD negativity by qPCR for BCR::ABL1 at the end of blinatumomab treatment. This patient has a b1a2 transcript (p190) and a presenting WBC of 150 × 103/μL. This patient continued to have low-level transcript (≤0.01%) at 2-year follow-up, with negative MRD evaluation by flow cytometry and FISH. NGS-based MRD is not available locally for further MRD evaluation. The rate of CRS was low at 17%, with no Grade 3-4 CRS. One patient developed grade 3 ICANS during induction with baseline CNS-negative disease. Thrombotic events were noted in 2 patients; one was line-associated, and the other was a stroke during ponatinib maintenance (15mg) and had full recovery. This patient is the only patient who discontinued ponatinib and was placed on dasatinib. Transaminitis was noted in 42% of patients, all grade 1-2. One patient developed hypertension while on maintenance ponatinib and was started on an antihypertensive. All patients completed 5 cycles of blinatumomab and continued on ponatinib, except for one patient, who was discussed earlier and switched to dasatinib. CNS-directed systemic therapy was given to 25% of patients at the end of blinatumomab cycles due to high risk for CNS disease. With a median follow-up of 22.5 months, OS and RFS remain 100%. Comparing overall survival with AYA-specific transplant outcomes (Supplement Table 1), no statistical difference was noted (Figure 1).

In this analysis, we noted a high response rate and MRD negativity in AYA patients treated with the combination of blinatumomab and ponatinib. Although with a short median follow-up of almost 2 years, no statistically significant survival difference was

observed compared with AYA-specific SCT outcomes. In both cohorts (blinatumomab/ponatinib and SCT), we observed a slight male predominance among AYA patients with Ph+ B-ALL (60%). Patients on high-dose ponatinib (30-45mg) were given a prophylactic dose of Apixaban. In our cohort, although the number was smaller and the follow-up relatively shorter compared to our SCT data, we noted no CNS or systemic relapses. Potential differences from prior reports that might have influenced the outcomes include a higher dose of ponatinib, which could lead to higher CNS concentrations. Additionally, all patients received 16 or more intrathecal chemotherapy, and 25% received CNS-directed systemic chemotherapy. No patient proceeded to transplantation, even in a patient with positive qPCR for BCR::ABL1.

Given the well-recognized psychosocial challenges in treating AYA patients, the outcomes have been inferior in real-world treatment settings compared to clinical trials. This was demonstrated in studies in the United States and the United Kingdom, in which a 2-year OS was reduced by 17.9%.(14, 15) This was primarily driven by lower adherence to long-term maintenance in acute lymphoblastic leukemia. In this AYA program, patients were offered SCT or stress compliance with ponatinib, with an understanding of their disease and the alternative therapy. Additionally, the simplicity of treatment (TKI-only maintenance) compared to traditional POMP maintenance in ALL is likely a contributing factor to patients' adherence. With this data, we think AYA patients can be successfully maintained on long-term maintenance, and in Ph+ B-ALL, therapy can be optimized with CNS-directed intensification, without the need for consolidative SCT.

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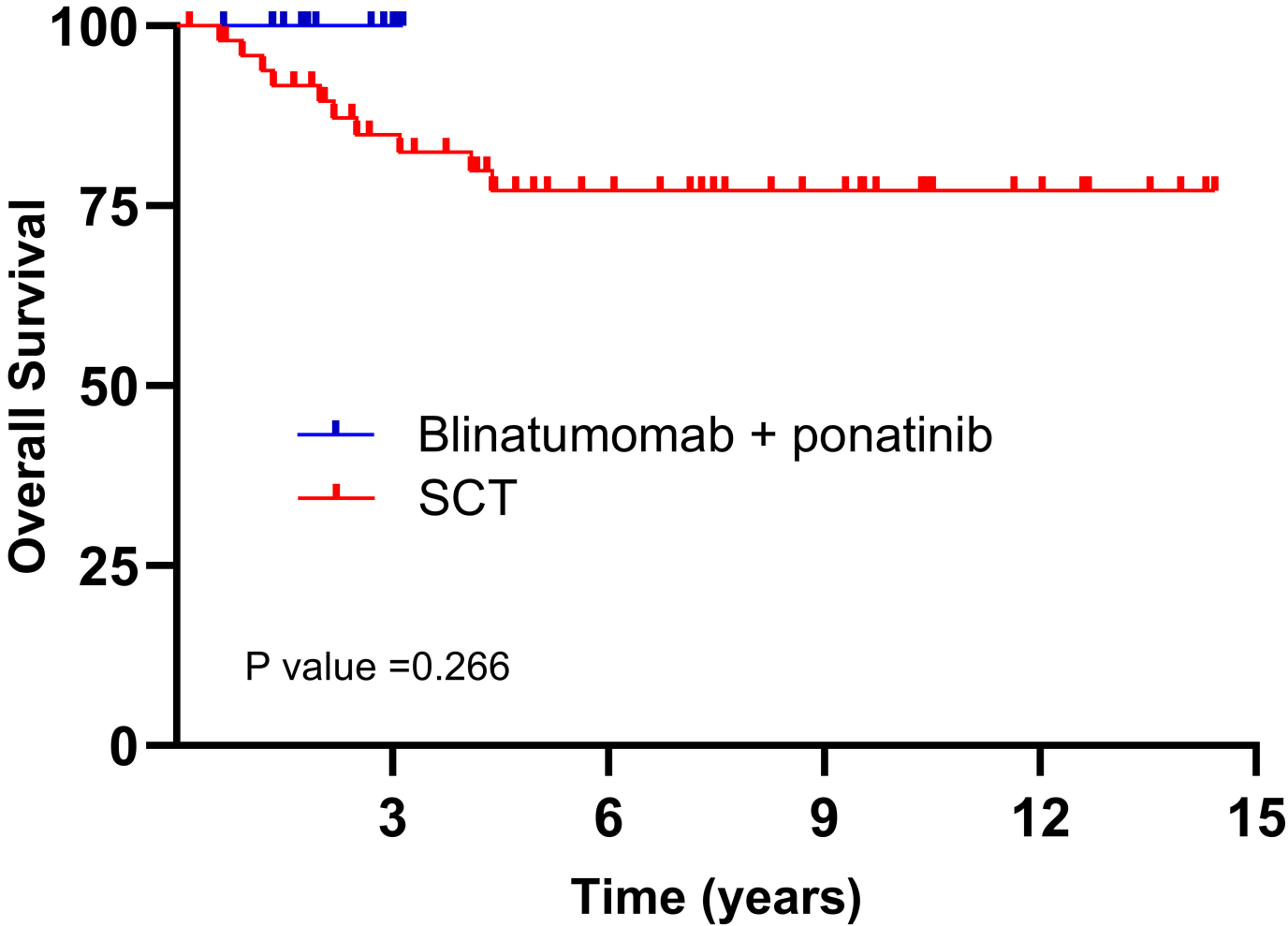
Table 1: Baseline characteristics, Response, and survival of adolescent and young adults with Philadelphia-positive B-ALL treated with blinatumomab and ponatinib.

Characteristic	**Blinatumomab/ponatinib (N =12)**
Age, y, median (range)	28.1 (16.2-45.2)
Female, n (%)	3 (25%)
ECOG, n (%)	
0	11 (91.7%)
1	0
≥ 2	1(8.3%)
WBC at diagnosis, n (%)	11(91.7%)
< 30000	3(25%)
≥ 30000-100000	4(33.3%)
>=100000	4(33.3%)
Not available	1(8.3%)
BM blasts, median (range)	70% (31%-92%)
CNS involvement, n *(%)*	1 (8.3%)
BCR::ABL p190 transcript, n (%)	5/8(63%)
Additional cytogenetic abnormalities, n (%)	4/9(44%)
Safety	
CRS (any grade)	2(17)
ICANs (any grade)	1(8)
Thrombosis	2 (17)
Overall response rate	12 (100%)
CR*	8/8 (100%)
CRi	0
CMR rate (PCR for BCR::ABL1)	
After induction	6(50%)
End of treatment	11(91.7%)
Survival	
2-year RFS	100%
2-year OS	100%

*Four patients were enrolled in the protocol in remission after 1-2 cycles of chemotherapy before referral.
Abbreviations: y, years; ECOG, Eastern Cooperative Oncology Group performance status; WBC, white blood cell (count); BM, bone marrow; CNS, central nervous system; BCR::ABL1, breakpoint cluster region–Abelson 1 fusion gene; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; CMR, complete molecular response; PCR, polymerase chain reaction; RFS, relapse-free survival; OS, overall survival.

Figure 1: Overall survival of adolescent and young adults (AYA) with Philadelphia-positive B-ALL treated with blinatumomab and ponatinib compared to AYA historical control of stem cell transplant in first remission.


100
75
50
25
0
Overall Survival
Blinatumomab + ponatinib
SCT
P value =0.266
3
6
9
12
15
Time (years)

Supplement Table 1: Baseline characteristics of 51 AYA patients treated with SCT in CR1 that were included as controls.

Characteristic	**SCT (N =51)**
Age, y, median (range)	26 (14-45)
Female, n (%)	22 (43.14%)
ECOG, n (%)	41 (80.4%)
0	35 (68.6%)
1	6 (11.8%)
≥ 2	0 (0%)
WBC at diagnosis, n (%)	40 (78.4%)
< 30000	20 (39.2%)
≥ 30000-100000	9 (17.6%)
>=100000	11 (21.6%)
Not available	11 (21.6)
BM blasts, median (range)	84.5% (20%-99%)
CNS involvement, n *(%)*	5 (9.8%)
BCR::ABL p190 transcript, n (%)	48 (94.12%)
Additional cytogenetic abnormalities, n (%)	26 (51%)
Induction regimen, n (%)	51 (100%)
Low intensity	12 (23.5%)
High intensity	39 (76.5%)
Blinatumomab	0
Frontline TKI, n (%)	51 (100%)
Imatinib	15 (29.5%)
Dasatinib	36 (70.6%)
Ponatinib	0
SCT	51 (100%)