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ORIGINAL ARTICLE

The efficacy of bortezomib during induction therapy in patients with high-risk acute lymphoblastic leukemia

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Abstract

Introduction: *Acute lymphoblastic leukemia (ALL) is characterized by the uncontrolled proliferation of lymphoid precursor cells, most from the B phenotype, which is the result of various cytogenetic mutations and alterations involved in cell division and survival.* **Objective:** *To evaluate the efficacy of bortezomib in patients with ALL through the measurable residual disease (MRD) outcome at 6 weeks (day +45) and response to induction therapy with chemotherapy in combination with a first-generation proteasome inhibitor.* **Material and methods:** *This was cross-sectional, observational, retrospective, and analytical study based on clinical records of patients diagnosed with ALL who received induction therapy plus bortezomib, from January 1, 2019, to May 31, 2024, and comparing it to a historic group.* **Results:** *Twenty patients were included, 60% (n = 12) of whom were male, with an average age of 26 years (range 18-61 years). All cases corresponded to the B phenotype, 85% were negative for BCR: ABL1, without central nervous system infiltration (CNS). After treatment initiation, the most common adverse event was anemia and thrombocytopenia (GIII-GIV) and 30% experienced grade I-II peripheral neuropathy. When compared to the historical record, the odds ratio (OR) to evaluate the treatment response with early response variables, there was no difference (confidence interval [CI] = 0.173-1.630, p = 0.206). In overall survival, there were no statistically significant differences when compared with the historical cohort, OR of 1.538 (CI = 0.502-4.748, p = 0.319).* **Conclusion:** *The addition of bortezomib to the induction chemotherapy did not show a benefit in the percentage of remissions or the proportion of MRD. It is important to continue exploring new options that can be added to this high-risk group of patients to reduce refractoriness and the proportion of early relapses.*

Keywords: *Acute lymphoblastic leukemia. Bortezomib. Measurable residual disease. Complete remission. Overall survival.*

Introduction

Acute lymphoblastic leukemia (ALL) is characterized by the uncontrolled proliferation of lymphoid precursor cells, most from the B phenotype, which is the result of various cytogenetic mutations and alterations involved in cell division and survival[1,2]. The treatment is based on the combination of different types of chemotherapy, with the main combination during induction being vinca alkaloids, anthracyclines, asparaginase, and steroids[3]. Generally speaking, treatment schemes are divided into adequate for adults or focused on a pediatric protocol, which uses a higher dose of chemotherapy with cycles of asparaginase[4,5]. Notably, the Hispanic population is afflicted with in a higher rate and also with a higher proportion of mutations considered of poor prognosis, such as those known as Philadelphia, along with the development at an adverse social setting[6,7]. When comparing the results with the world,

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the rate of responses in our region is lower, due to a high rate of mortality during the induction period, as well as limited access to strategies such as the bi-specific, hematopoietic progenitors transplant, and immunotoxins (Blinatumomab and inotuzumab)[8,9].

The options for treatment failure are also limited since the rescue is still based on high doses of chemotherapy (FLAG and FLAG-IDA)[10,11]. Due to this, ERM is the main prognosis factor, not only to prevent relapse but also to modify the intensity of the treatment through innovative options such as blinatumomab, inotuzumab, or the therapy based on CAR-T[12,13]. Along with somatic mutations, the limited access to methods to determine the standardized EMR, the Hispanic population also suffers a limited access to treatment therapies, which causes an excess in mortality (25-35% in the pediatric population), as well as a non-negligible quantity of treatment desertion[14]. This has required a selection of accessible and affordable strategies that can be combined with different chemotherapy schemes. Other than chemotherapy, very few drugs are considered adequate to be combined with the treatment of ALL. Bortezomib is a first-generation proteasome inhibitor widely used in the treatment of blood dyscrasias, such as multiple myeloma, or mantle cell lymphoma[15,16]. Nevertheless, in ALL cell lines (MOLT-4), a synergic effect has been proven to stop the cell cycle and maintain the cells in G1, inducing their apoptosis[17]. Bortezomib has been combined with different drugs used during the induction (vincristine, prednisone, pegylated asparaginase, and doxorubicin), which improves the results in specific subgroups such as T-ALL; however, the experience in adult ALL schemes is still limited[18,19].

The response rate (CR) in patients considered to be high risk (age, hyperleukocytosis, cytogenetic abnormalities, or mutations) is limited. Due to this, the effect of the inclusion of the first-generation proteasome inhibitor bortezomib in the chemotherapy scheme was analyzed on the rate of CR as well as the negativity of the measurable residual disease (MRD).

Materials and methods

A retrospective, observational, and analytical study was carried out on clinical records of patients exposed to bortezomib during the induction therapy treated at the Hospital General de México "Dr. Eduardo Liceaga," who have been diagnosed with high-risk ALL from January 1, 2018, to May 31, 2024, and who met the following inclusion criteria: (1) both genders, (2) > 18 years of age, (3) underwent systemic chemotherapy treatment with bortezomib, and (4) MRD results through multiparametric flow cytometry at the end of induction. Patients with BCR: ABL1 were included. Exclusion criteria were as follows: (1) ECOG > 2, (2) diagnosis of phenotypic or bilinear leukemia, (4) palliative scheme or transfusion support, and (5) severe comorbidities that could jeopardize the therapy.

Chemotherapy treatment

The most used chemotherapy scheme was CALGB modified to include vincristine (1.2 mg/m^2 per body surface area) on days 1, 8, 15, and 22 of the treatment; daunorubicin was administered in 25 mg/m^2 per body surface area on days 1, 8, 15, and 22. The pegylated asparaginase was substituted by synthesized asparaginase of E. coli at a dose of 5000 UI/m^2 per body surface area in 6 doses starting at day +5 of the chemotherapy. Prednisone was administered at 100 mg/day as a fixed dose. Intracranial chemotherapy was included following CALGB10403[20]. In older individuals, the most used scheme was the hyper-CVAD scheme[21].

The administration of bortezomib was subcutaneous at 1.3 mg/m^2 per body surface area on days 1, 4, 8, and 11; when it coincided with the administration of vincristine, the administration of bortezomib was carried out to the next day.

The toxicity of the scheme was evaluated following NCI common toxicity criteria for adverse events version 4.016; grade 4 cases were considered as having severe toxicity. In case of severe toxicity (grade 3 or grade 4) associated with bortezomib, the administration was halted for the following cycles.

Procedure

Once the patients met the inclusion criteria, they were followed post-induction chemotherapy. The follow-up took place during the outpatient visit, where their clinical and biochemical indicators, as well as prognosis factors. The final MRD was carried out with samples obtained from the bone marrow, extracting 5 mL of blood from the bone marrow, subsequently placing them in EDTA tubes, and analyzed through flow cytometry, which used the markers for detection of lymphoid blast on the expression of CD19, CD10, and CD34+.

Statistical analysis

The sample size was estimated using a Goodness-of-Fit formula, based on the expected effect size

compared to the effect size reported in other similar studies. The sample size calculation was performed using the G-Power 3.1.9.2 tool. From the calculated effect size of 0.8, a sample size of 21 patient records was obtained for the study.

To describe the demographic variables, the Shapiro-Wilk test was used to estimate the normality of distribution in the numeric variables. To determine the relationship between the main variables and the main outcomes (time until the next treatment and overall survival), we calculated the odds ratio. In addition, we used Kaplan-Meier estimates to analyze the time until the next treatment and overall survival. Regardless of the median value, differences between groups were analyzed with a Log-Rank test, and the data were presented in median values. We established $p < 0.05$ as a statistical difference. We conducted all statistical analyses using the SPSS version 27 (SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp) software and generated figures using GraphPad Prisma version 7.

Ethical consideration

For this study, we used clinical records only. Therefore, informed consent was not necessary. The researchers involved in the study confirm that all ethical aspects of privacy and confidentiality have been met while dealing with retrospective information. This retrospective cohort study was carried out following the Helsinki Declaration and approved by the Biosecurity, Ethics, and Research Committee of Hospital General de México "Dr. Eduardo Liceaga," under the protocol number (DECS/UPO-CT-2296-2024).

Results

A total of 20 patients diagnosed with high-risk ALL were studied during induction therapy at the Hematology Department of the Hospital General de Mexico "Dr. Eduardo Liceaga." Most patients were male (n = 12), with an average age of 26 years (Range 18-61 years). Morphological analysis according to FAB classification showed all cases (n = 20) were classified as L2 subtype, with an average blast count of 82% on microscopic examination at diagnosis. Flow cytometry analysis according to EGIL classification categorized them as BI immunophenotype 10% (n = 2), BII 85% (n = 17), and BIII 5% (n = 1). Regarding the Philadelphia chromosome, 15% (n = 3) tested positive, 5% (n = 1) were undeterminable, and 85% (n = 17) tested negative. Patients with positive results received first-generation tyrosine kinase inhibitors (imatinib) added during the induction therapy. Cytogenetic testing was requested for all patients; however, 60% (n = 12) had undeterminable samples, 20% (n = 4) had a normal karyotype, 15% (n = 3) had complex karyotypes, and 5% (n = 1) had hypodiploidy. No patients presented central nervous system infiltration at diagnosis. The leukocyte counts at diagnosis classified 20% of patients as high risk ($> 30 \times 10^3/\mu L$).

Comorbidities at the time of diagnosis included three patients with systemic arterial hypertension (15%), one with hypothyroidism (5%), one with type 1 diabetes mellitus (5%), and one patient with absence seizures (5%). Most patients had a normal BMI, with 15% classified as overweight or grade I obesity. The most used chemotherapy scheme for induction was CALGB10403 in 70% (n = 14) of cases, 15% (n = 3) received the hyper-CVAD scheme, and the remaining 15% (n = 3) received an induction based on weekly administration of doxorubicin, vincristine, and 28 days of prednisone. One patient receiving CALGB10403 had rituximab added to their scheme due to CD20 positivity.

Adverse effects and complications

During induction therapy, grade IV myelotoxicity was found, characterized by anemia, thrombocytopenia, and neutropenia. Peripheral neuropathy was one of the most frequent adverse events with bortezomib, observed in 30% (6) of patients, classified as grade I-II. Gastrointestinal manifestations occurred in 15% (3) of patients, with diarrhea being the most frequent symptom at grade I. Liver enzyme elevation was observed in 10% (2) of the cases, with one case categorized as grade IV acute liver failure following chemotherapy. Finally, 5% (1) presented asymptomatic hypofibrinogenemia.

During hospitalization, 25% (5) of patients developed febrile neutropenia, 15% (3) were diagnosed with nosocomial pneumonia, 10% (2) had influenza pneumonia confirmed by RT-PCR testing, and 15% (3) showed evidence of bacteremia with isolation of *Staphylococcus aureus*, *Escherichia coli*, and *Acinetobacter baumannii* in blood cultures. Chronic cavitary aspergillosis was diagnosed, confirmed by positive galactomannan in bronchoalveolar lavage in 10% (2) of patients. Two patients died during induction therapy due to septic shock complicating bacteremia caused by acinetobacter baumannii and influenza pneumonia.

Comparison of outcomes between the bortezomib group and the historic group

Clinical outcomes of patients treated with bortezomib (n = 20) were compared with those of a historic group of patients with ALL treated at the same center between 2022 and 2024 (n = 33) who did not receive bortezomib during induction therapy to achieve remission.

The response proportions to induction showed no significant difference between both cohorts (p = 0.137). In the cohort that received bortezomib, 55% of the population (n = 11) had an early complete response compared to 73.5% (25%) of the population that did not receive bortezomib. Regarding the MRD results, the test could not be performed in all patients in the cohort, however, in the group that received bortezomib, only two (12.5%) of 16 patients showed a negative MRD post-induction, in comparison with the group that did not receive bortezomib, where 12 (70.5%) of 17 patients were reported. The proportion comparison analysis could not be performed because the rule of a minimum of five patients per study variable was not met.

OR was used to assess the treatment response between the two groups, with bone marrow aspirate as the response variable, yielding an OR of 0.532 (confidence interval [CI] = 0.173-1.630, p = 0.206), indicating no statistically significant difference. Regarding MRD results, the test could not be performed in all patients in the historic group; however, in the bortezomib group, only 2 (11.1%) out of 18 patients achieved negative MRD post-induction. A comparison of proportions analysis could not be conducted due to not meeting the minimum rule of five patients per study variable. When comparing overall survival between the two groups, there were no statistically significant differences, with an odds ratio (OR) of 1.538 (CI = 0.502-4.748, p = 0.319).

The median survival for the bortezomib group was 96 days (range 26-373 days), compared to the group that did not receive bortezomib which was 91.50 (range 25-327), this difference did not show statistical significance (0.778). On the other hand, the Kaplan-Meier survival curve was estimated for both groups, and a log-rank (0.104) was obtained from the Mantel-Cox test. The curve is shown in figure 1.

Early treatment response

Two clinical parameters were used to assess early treatment response: the first was established through response to pre-induction steroids, where 50% (10) of patients presented a response with lymphocyte count on complete blood count of less than $1 \times 10^3/\mu L$, while the remaining 50% (10) did not show this response. Another measure was through MRD on day +8 of the induction therapy with bortezomib; 25% (n = 5) had less than 5% blasts, whereas 45% (n = 9) had more than 5% blasts, and the remaining had hemodiluted BMA without blast evidence. The relapse proportions in this population were 70% (n = 14).

The early treatment response was contrasted with the overall survival and induction response between the bortezomib and non-bortezomib groups. The response to corticosteroids yielded an OR of 1.063 (95% CI = 0.350-3.227, p = 0.570), which did not reach statistical significance. Regarding MRD on day +8, the outcome OR was 1.299 (95% CI = 0.426-3.958, p = 0.430), considered not statistically significant. Figure 2 displays a Forest plot illustrating the effect of bortezomib on clinical outcomes.

Discussion

Throughout the years, attempts toward improving the induction treatment have been made, focusing on adding drugs when a therapeutic target exists, such as the expression of CD20 in lymphoblasts, or the positivity for BCR: ABL1. The best example is the hyper-CVAD scheme which has forgone multiple modifications since its creation[22,23]. Similar to this scheme, CALGB10403 has also been modified, especially in our country, due to the lack of pegylated asparaginase, and because it is substituted with an asparaginase derived from *Escherichia coli*. Despite these modifications, the rate of complete remissions at 4 weeks remains above 80%, which makes it a plausible option in countries with limited resources[9].

The main objective of this study was to evaluate the effect of the proteasome inhibitor addition on the rate of complete remissions, and the negativity of MRD at 6 weeks of treatment in patients considered to be high risk. This population was of interest to us since, in the Hispanic population, most of the patients are considered to have a high risk of relapse diagnosis, as well as a lower rate of complete remissions[24]. In line with the literature, the patients considered high-risk present a complete remission rate slightly lower than those of standard risk (90% vs. 97%, with a survivability rate at 5 years of 29%)[9]. Similar to this, in the CALGB10403 protocol, individual factors like the leukocyte count ($> 30 \times 10^3$/mcl) had an impact on the survivability (HR = 1.85, 1.14-3.01, 95% CI), but other variables, like being of Hispanic origin, did not present a substantial effect[20].

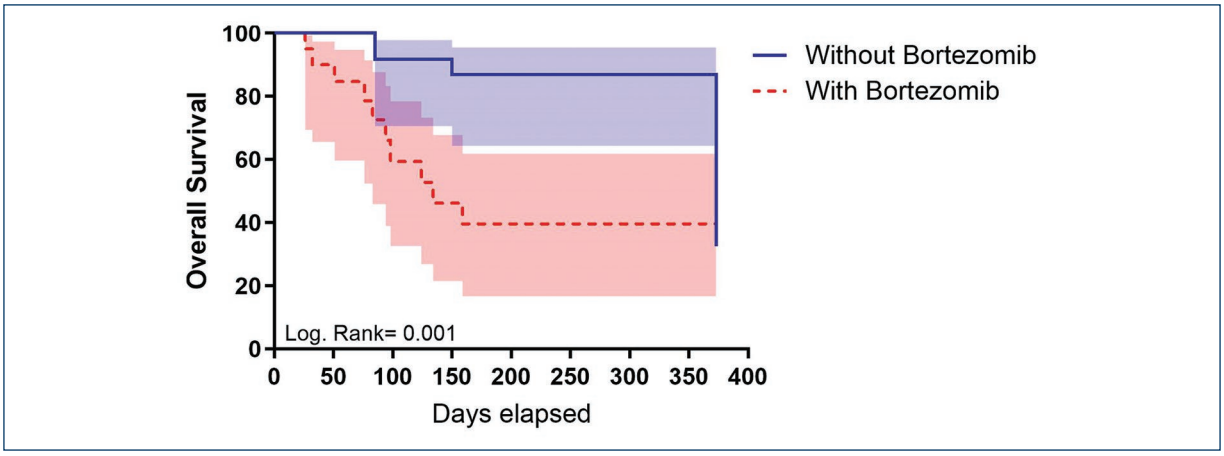

Figure 1. Kaplan-Meier plot comparing the study group (with Bortezomib) and the historical cohort (without Bortezomib).

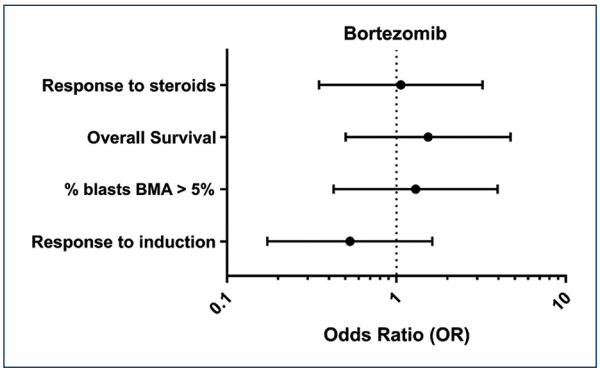

Figure 2. Forest plot on the effect between the main clinical outcomes and the early response.

In this study, we compared treatment response and overall survival between patients treated with bortezomib during induction therapy and a historic group without bortezomib. There was no statistically significant difference in terms of MRD and response at 4 weeks. In Jain et al.'s study, which included CD20+ Ph-negative B-ALL patients, ages up to 20 years, they received a modified BFM-90 scheme with rituximab and bortezomib, achieving a negative MRD in 70.9%, contrasting with our study where only 11.1% had a negative MRD[22]. In Jonas et al phase I study, evaluating newly diagnosed Ph-negative B-ALL patients aged 18-64 years, they used hyper-CVAD plus carfilzomib as induction, achieving a 90% CR rate post-first cycle using MRD assessment[24]. Notably, the addition of anti-CD20 monoclonal antibodies in previous studies suggests that better treatment response rates may be attributed to synergy with this medication.

One factor potentially influencing our results is the age of the sample; in scientific evidence, the population studied comprises children and adolescents due to pharmacokinetic considerations, with rapid proteasome 20S activity inhibition observed immediately after drug administration in adults, contrasting with higher plasma concentrations in the second week in pediatric populations[16]. Another crucial consideration is the ethnicity of patients; studies by Jonas and Iguchi conducted predominantly in Caucasian and Asian populations, respectively, demonstrated treatment responses to Bortezomib[25,26]. Most chemotherapy schemes are developed in the United States and Europe, underscoring the importance of adapting them to the predominantly Hispanic population of Mexico. Basqueira et al. reported complete responses ranging from 64.2% to 79.5% depending on the scheme used, in contrast with other Latin American countries where responses were mostly above 85%. The study reported a 17% non-adherence rate among adult ALL patients, with electronic health records cited as contributing factors[9].

Early response evaluation through pre-induction steroids and day +8 MRD was compared between the bortezomib and non-bortezomib groups, showing no substantial evidence. Literature variations include blood peripheral MRD assessment at day +8, showing a similar 50% response. In Ramos et al.'s study, factors associated with induction therapy response were evaluated, showing associations with steroid response and day +8 response ($p = 0.0045$ and 0.0023)[27].

Adverse effects and complications secondary to chemotherapy were consistent with historical records and Iguchi et al study, where no severe adverse effects

necessitating treatment discontinuation were observed[25]. Ramos et al. did not report neurotoxicity events, contrasting with our study where six cases of grade I-II peripheral neuropathy were managed with gabapentinoids, associated with patient age[28].

In our study, two patients died during induction therapy due to infectious processes compared to August et al.'s study, where three patients died due to chemotherapy toxicity[29]. In the TACL phase II study, three out of 22 patients died due to bacterial sepsis[30]. This emphasizes that the implementation of health programs for timely antibiotic therapy initiation is crucial.

It can be considered that despite *in vitro* synergistic activity, assessing the efficacy of proteasome inhibitors *in vivo* remains challenging as most schemes involve more than two drugs. Evaluating efficacy in relapse and MRD appears to be more beneficial, whereas our study did not demonstrate improvement in increasing remission rates or cases with negative MRD, maintaining the risk of infectious processes or neurological adverse events. Despite all patients receiving antifungal and antiviral prophylaxis, viral reactivation risk and potential vincristine-associated neurological events remain latent. Ultimately, it is proposed that first-generation proteasome inhibitors do not show clear utility when added to first-line schemes, but may be beneficial in achieving negative MRD.

Conclusion

Treating adult ALL remains challenging due to lower response rates compared to pediatric populations. The Latin American population, in particular, exhibits high biological risk factors such as Ph-like abnormalities, and a higher proportion of factors predisposing to relapse or treatment failure. Our objective was to identify whether adding bortezomib to the treatment scheme could improve response rates. Contrary to expectations, the addition of bortezomib did not affect responses, leading us to consider it not useful for induction therapy in ALL. Improvements are still needed in referral systems and the availability of more effective drugs such as bi-specific therapy or immunotoxins. Finally, we propose that bortezomib could potentially be used in other stages of the treatment, such as positive MRD, T-cell precursor leukemias, or through new clinical trials.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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