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Research paper

Comparison of intensive, pediatric-inspired therapy with non-intensive therapy in older adults aged 55–65 years with Philadelphia chromosome-negative acute lymphoblastic leukemia

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ABSTRACT

Background and objective: The standardization of treatment of older adults with Philadelphia chromosome negative (Ph-) acute lymphoblastic leukemia (ALL) is challenging, especially in the age range of 55–65 years. This study aimed to compare intensive, pediatric-inspired therapy with non-intensive therapy in this population of patients.

Patients and methods: The outcomes of 67 patients prospectively included in two consecutive pediatric-inspired intensive protocols (ALL-HR03 and ALL-HR11) from the Spanish PETHEMA Group were compared with those from 44 patients included in a contemporary semi-intensive protocol (ALL-OLD07).

Results: Baseline patient and ALL characteristics were similar in both groups, except for a younger median age in the intensive group (medians: 58 vs. 62 years). Patients treated intensively had a higher complete remission rate (85% vs. 64%, p = 0.005), a lower cumulative incidence of relapse (39% [95%CI, 25% to 52%] vs. 60% [95%CI, 38% to 77%], p = .003), a similar cumulative incidence of treatment-related mortality (28% [95% CI, 18%, 40%] vs. 21% [95% CI, 10%, 34%]) and superior event-free survival at 2 years (37% [95%CI, 25%–49%) vs.

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21% [8%-34%], p = 0.002). On multivariable analysis the type of protocol was the only variable with independent significance for event-free survival (HR [95% CI]: 2 [1.3, 3], p = .002).
Conclusions: Compared with less intensive chemotherapy, pediatric-inspired intensive chemotherapy significantly improves the outcome of older adults with Ph-negative ALL in the age range of 55–65 years.

1. Introduction

The results of the treatment of Philadelphia chromosome (Ph)-negative acute lymphoblastic leukemia (ALL) in adults have improved in recent years [1]. The use of pediatric-like protocols in the younger adult (YA) population partially explains this improvement. Intensified pediatric-inspired regimens with continuous dose-intense exposure to chemotherapy and higher cumulative doses of non-myelotoxic drugs such as L-asparaginase and glucocorticoids are currently used by most groups to treat ALL in adult patients [2,3]. However, the definition of the population likely to benefit from a pediatric-like approach remains controversial, especially for the upper age limit for using these pediatric-based protocols. In fact, this limit ranges from 30 years to 55 years among the different studies [4–12]. As treatment compliance and tolerability worsens in patients older than 55 years, treatment of these patients remains a challenge, especially for those aged between 55 and 65 years, in whom a balance between effectiveness and toxicity is difficult to assess. This explains the lack of standardization of the treatment of these older patients in current clinical practice, where the election between intensive, pediatric-inspired versus semi-intensive therapy is frequently individualized according to physicians and/or patients pReferences

Although in the protocols of the Spanish PETHEMA (Programa Español de Tratamientos en Hematología) Group intensive chemotherapy based on high-risk ALL protocols is recommended for fit adults aged 55–65 years, the final decision is taken by the participating physicians. As specific analyses of outcomes according to the intensity of the therapy in the age group of 55–65 years are scarce [13], the aim of this study was to analyze and compare the baseline characteristics, the results of treatment and the outcomes of older adults (55–65 years) with Ph-negative ALL included in two consecutive intensive pediatric-based protocols vs. those from one concurrent semi-intensive protocol from the PETHEMA Group.

2. Patients and methods

2.1. Patients and diagnostic criteria

Older adult patients aged 55–65 years with Ph-negative ALL prospectively included between 2003 and 2017 in two consecutive pediatric-inspired intensive protocols (ALL-HR03 (from 2003 to 2011) and ALL-HR11 (from 2011 to 2017), ClinicalTrials.gov Identifier: NCT00853008 and NCT01540812, respectively) or in one semi-intensive protocol (ALL-OLD07 [from 2007 to 2017], ClinicalTrials.gov Identifier: NCT 01366898) from the Spanish PETHEMA Group were analyzed in this study. The ethics committee or institutional review board of each participating center approved these studies. All patients were centrally registered at the PETHEMA data center, and this center was also responsible for collection and analysis of the information.

Diagnosis of ALL was performed by morphological analysis of bone marrow (BM) specimens along with immunophenotyping using monoclonal antibodies reactive with B-cell, T-cell, myeloid and precursor cell- associated antigens. Chromosomal analyses were performed in institutional laboratories, and results were centrally reviewed. Central nervous system (CNS) involvement was assessed by the presence of lymphoblasts in samples of cerebrospinal fluid (CSF). In the ALL-HR03 and ALL-HR11 protocols BM minimal residual disease (MRD) levels were assessed at the end of induction (weeks 5–6) in CR patients and at the end of the third early consolidation cycle (weeks 16–18) by 4-color (ALL-HR03) or 8-color (ALL-HR11) multiparameter flow cytometry (MFC) [14]. MRD levels at these points were used to assign post-consolidation therapy (delayed intensification and maintenance or allogeneic hematopoietic stem cell transplantation [HSCT]) [15,16]. MRD study was not performed in the ALL-OLD07 trial.

The ALL-HR03 and ALL-HR11 protocols were pediatric-based trials enrolling patients aged 18–55 years with Ph-negative ALL with high-risk criteria based on age, WBC counts, phenotypic and/or cytogenetic features. Inclusion of patients aged 56–65 years was recommended if the patients were considered suitable for receiving intensive chemotherapy by the participating physicians. The ALL-OLD07 trial included patients over 55 years with a Charlson Comorbidity Index less than or equal to 3 and an Eastern Cooperative Oncology Group (ECOG) score lower than 3 except if poor performance status was attributable to ALL. The results of the ALL-HR03 and the ALL-OLD07 have been fully published [15,16] and the preliminary results of the ongoing ALL-HR11 have been presented in abstract form [17].

2.2. Treatments and response assessment

The treatment phases of the ALL-HR03 and ALL-HR11 protocols comprised a pre-phase, a first induction, an optional second induction if no complete response (CR) was attained after the first one, early consolidation (3 cycles), delayed consolidation (3 cycles), maintenance with reinductions up to the first year in first CR and maintenance without reinductions until two years from the date of CR [15,16]. Patients with poor early response or without adequate MRD clearance were allocated to allogeneic HSCT. Given that the design and the chemotherapy schedule of both protocols is similar they were considered together in this study. In turn, the ALL-OLD07 trial comprised a pre-phase, induction 1 and 2, consolidation, maintenance with reinductions during the first year and maintenance without reinductions during the second year [17]. Allogeneic HSCT was an option for fit patients in first CR after consolidation. The CNS prophylaxis was identical in the three trials and consisted of triple intrathecal therapy (14 administrations). Supplemental Table 1 shows the cumulated doses of each cytotoxic drug in the three protocols.

Response was assessed by BM aspirate at the end of induction. CR was defined as: absence of extramedullary disease, neutrophils > 1×10^9/L, platelets > 100×10^9/L, and < 5% BM blast cells. Resistant disease (RD) was defined as leukemia persistence in patients surviving induction. Early death (ED) was defined as death occurring before achieving CR. Relapse was defined as disease recurrence at any site after achieving CR. Disease-free survival (DFS) was calculated from the date of CR until the date of first relapse or death in CR by any cause. Overall survival (OS) was measured from the time of diagnosis to the time of death or last follow-up. Event-free survival (EFS) was calculated from the date of diagnosis to the date of death in induction, failure of CR attainment, relapse, or death by any cause or last follow-up.

2.3. Statistical analysis

The main clinical and hematologic variables of ALL patients included in each protocol were compared by the non-parametric median test (continuous variables) and the chi-square or Fisher's exact tests (categorical variables). DFS, OS and EFS curves were plotted by the Kaplan and Meier method and compared by the log-rank test, whereas multivariable analyses were performed using the Cox proportional hazards regression model. No imputation method was used for missing