612. ACUTE LYMPHOBLASTIC LEUKEMIA: CLINICAL STUDIES:
ADVANCES IN THE TREATMENT OF ALL | DECEMBER 07, 2017

A Treatment Protocol with Imatinib and Intensive Chemotherapy for Pediatric Philadelphia Positive Acute Lymphoblastic Leukemia Patients: A Single-Arm, Intergroup Study (EsPhALL 2010-2014)

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Blood blood **(2017) 130 (Suppl_1) : 97.**

http://doi.org/10.1182/blood.V130.Suppl_1.97.97

Abstract

Introduction. Approximately 3-5% of pediatric ALL patients present with the Philadelphia chromosome (Ph+). In the past, Ph+ ALL was associated with a poor prognosis, with long-term event-free-survival (EFS) rates of approximately 30% and most patients allocated to hematopoietic stem cell transplantation (HSCT) in first complete remission (CR1). The COG AALL0031 study showed that continuous high imatinib exposure improved outcome with no increase in toxicity and that HSCT offered no advantage over intensive chemotherapy plus imatinib (Schultz et al, JCO2009). Contemporarily, the EsPhALL 2004-2009 intergroup study of post-induction treatment of Ph+ ALL randomly tested the discontinuous use of imatinib added to BFM ALL high risk chemotherapy after the Induction phase in patients with early response, showing an approximate 10% advantage in long-term DFS. All non-responding patients received imatinib and overall 80% received HSCT in CR1 (Biondi et al, Lancet Oncology 2012). Based on both studies, in 2010 the EsPhALL trial was amended into a single arm study to give all patients, on top of the BFM ALL high risk chemotherapy, imatinib 300/mg/m^2/day continuously since day 15 of Induction and to gradually decrease the use of HSCT. We present here the results of this EsPhALL 2010-2014 study.

Methods. Ph+ ALL patients aged 1-17 years were enrolled by 10 national study groups (AIEOP, BFM-G/CH, COALL, FRALLE-EORTC, NOPHO, MRC, DCOG, CPH, PINDA, and HKPHOSG), mainly in Europe. MRD was assessed by PCR using IG/TR targets or BCR/ABL1 in hierarchical order, according to Euro-MRD rules. Eligibility to HSCT depended on early response and, after 2012, on MRD at end of Protocol IB ($\geq 5 \times 10^{-4}$) and at the end of consolidation block 3 (any positivity in patients with MRD$< 5 \times 10^{-4}$ at end of IB). Imatinib was recommended throughout the first year after transplant. Patients who continued on chemotherapy received treatment until 24 months after diagnosis.

Results. Overall 158 patients were registered from January 2010 to December 2014; 3 were not eligible, leaving 155 evaluable patients. Sixty-two patients (40%) were ≥ 10 years, 73 (47%) had ≥50,000 WBC count at diagnosis, 103 (84%) had p190. 102 (66%) patients achieved both early good response and CR1 at end of IA and were classified as good risk, while the remaining 53 (34%) were at poor risk. CR1 was achieved by 151 patients (97%) at the end of Induction and by the remaining 4 at the end of IB. Overall, 59 patients (38%) underwent HSCT in CR1. Nineteen patients discontinued treatment, 17 during chemotherapy, 15 due to serious adverse events (SAE, of which 9 related to imatinib - mainly infections)

and the remaining 2 to MRD increase (1) and to transfer to adult unit (1). Among patients who underwent HSCT in CR1, 2 discontinued imatinib after HSCT, due to MRD increase (1) and gastrointestinal toxicity related to imatinib (1). Overall, 185 SAE were observed in 86 (55%) patients. The most frequent SAE was infection which occurred in 50 (32%) patients. Other toxicities included osteonecrosis (7 patients, 5%) and gastrointestinal disorders (9 patients, 6%). On the complete cohort of 155 patients, with a median follow-up of 57 months (range 1-86), the 5-year EFS and survival were 57.0 (SE 4.1) and 71.8 (SE 3.8), respectively. The 5-year cumulative incidence of relapse was 26.9 (SE 3.7). Overall, 65 events occurred, 46 in 96 patients who received chemotherapy only (32 relapses and 14 deaths in CCR) and 19 in 59 HSCT in CR1 (8 relapses and 11 deaths in CCR). Overall, relapses occurred in the BM (22), BM+CNS (11), BM+eye (1) and CNS (6). All deaths in CCR, except for 1 in chemotherapy and 3 after HSCT, were due to infection. Half of the deaths in CCR (12/25) occurred in 2 unexpected clusters, in HSCT performed in 2010-2011 and in chemotherapy-only patients ≥ 10 years. Further investigations did not reveal any common pattern within the clusters.

Conclusions: Addition of imatinib given continuously since day 15 of induction markedly increased CR rate to 97% from 50% of the EsPhALL 2004-2009 study. Moreover, in EsPhALL 2010-2014 only 38% of patients underwent HSCT in CR1 (decreasing from 56% in 2010 to 28% in 2014), compared with 81% in the previous study. In spite of this marked decrease in HSCT, the outcome was similar in the 2 studies: 5-year EFS and survival were 57.0% and 71.8% versus 60.3% and 71.6%, respectively in EsPhALL 2010-2014 versus EsPhALL 2004-2009.

Disclosures

Cazzaniga: *Fondazione Tettamanti onlus:* Employment; *Italian Association for Cancer Research:* Research Funding. **Saha:** *Shire:* Research Funding. **Schrappe:** *Medac:* Consultancy, Research Funding; *SigmaTau:* Consultancy, Research Funding; *Novartis:* Consultancy, Research Funding; *JAZZ Pharma:* Consultancy, Research Funding; *Baxalta:* Consultancy, Research Funding.

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*Asterisk with author names denotes non-ASH members.


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