(S103) REPLACEMENT OF HIGH DOSE COMBINATION CHEMOTHERAPY WITH BLINATUMOMAB IN NEWLY DIAGNOSED PEDIATRIC HIGH-RISK B-CELL ALL IMPROVES EFFICACY AND SAFETY IN THE RANDOMIZED PHASE 3 AIEOP-BFM ALL 2017 TRIAL

Topic: 02. Acute lymphoblastic leukemia - Clinical

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Background

The bispecific T-cell engager Blinatumomab, targeting CD19 expressed on leukemic cells, may offer an option to safely reduce chemotherapy, while improving anti-leukemia efficacy in newly diagnosed pediatric patients with high-risk (HR) B-cell acute lymphoblastic leukemia (ALL).

Aims

The primary objective of this trial was to determine whether the event-free survival (EFS) in children with HR ALL could be improved by at least 10% by replacing two highly intensive conventional chemotherapy courses (HR-2', HR-3') with two 28-day cycles of blinatumomab (plus 2 doses of intrathecal methotrexate per cycle). Secondary study objectives were: i) To assess whether life-threatening treatment-related complications and mortality could be reduced in the experimental blinatumomab arm (EA) compared with the chemotherapy control arm (CA) ii) To determine the proportion of patients with inadequate response based on minimal residual disease detection (MRD) in the two treatment arms.

Methods

Following induction, consolidation, and one intensive chemotherapy course (HR-1`), 92.3% of 768 eligible patients were randomized to receive either the EA (n=358) or the CA (n=351) arm.

Results

Baseline patient characteristics were balanced between the two randomized groups. A large proportion of patients presented with adverse genetic characteristics, such as hypodiploidy or *KMT2A* rearrangement, or were found to have an inadequate response to early treatment. Overall, 10% of HR patients had an indication for allogeneic hematopoietic stem cell transplantation (SCT) in first complete remission (CR1), mainly due to high end-consolidation MRD levels. A planned interim analysis (74% of target events reported, boundary of the interim analysis p-value = 0.031) revealed that the 4y-EFS was 83.0% (SE 2.5%) in the EA versus 70.3% (SE 3.1) in the CA arm (intent-to-treat analysis, p-value 0.0002), corresponding to an estimated hazard ratio (Cox model) of 0.51 (95% CI: 0.35-0.73) for EA compared to CA (2.9 years of median follow-up). The cumulative incidence of relapse (CIR) was 11.8% (SE 2.2%) in the EA (n= 31 relapses) as compared to 21.4% (SE 2.9%) in the CA (n=57). Remarkably, the rate of isolated CNS-relapse was 0.3% in the EA (n=1) while it was 2.5% in the CA (n=9). Patients still MRD-positive before randomization decreased their MRD load in 76.9% if treated with Blinatumomab, but only in 45.8% if treated with chemotherapy (p-value <0.0001). Toxicity profiles during the randomized treatment phase differed significantly between EA and CA – in favor of the EA: Clinically relevant infectious adverse reactions occurred in 69.4% of CA patients versus 22.8% in the EA (p<0.001). Neurologic adverse reactions were reported in 2.9% of the CA group and 11.7% in the EA (p<0.001). In the CA, 10% of the patients were hospitalized for severe mucositis/stomatitis versus 0.3% in the EA. Cytokine release syndrome ≥ grade 2 was rare in the EA (1.1%). Sixteen patients (4.7%) had 17 life-threatening adverse reactions in the CA versus one in the EA (as well fatal, 0.3%). Among transplanted patients, the non-relapse mortality was 16% in the CA (n=12/73) compared with 2.5% in the EA (n=2/79).

Summary/Conclusion

For the first time, in newly diagnosed ALL, highly toxic chemotherapy elements have successfully been replaced by blinatumomab demonstrating a safer but also superior anti-leukemia efficacy of immunotherapy in prognostically unfavorable pediatric B-ALL.