TYROSINE KINASE INHIBITORS MANAGEMENT AFTER ALLOGENEIC STEM CELL TRANSPLANTATION FOR PH+ ALL: LESSONS FROM A PEDIATRIC CHALLENGING CASE

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Introduction: Philadelphia chromosome is found in less than 5% of pediatric but in more than 20% of adults patients with acute lymphoblastic leukemia (ALL). The advent of tyrosine kinase inhibitors (TKIs) lead to a dramatic improvement in the prognosis of these patients, who now have the same stem cell transplantation (SCT) indications as other ALL patients. Recommendations regarding the choice between prophylactic or preemptive strategy, duration of use and the best type of TKI post-SCT need to be better defined. **Objectives:** Here we aimed to report a Ph+ ALL pediatric case and to discuss TKI management after SCT. **Case report:** An 9-year-old boy, diagnosed with hyperleukocytic Ph+ B-ALL,mutated *IKZF1* and negative CNS was treated according to EsPhALL 2010 protocol. He was poor steroid responder on D8, started imatinib on D14, had 30% of blasts on D15 and 0,4% on D33, persistent positive MRD 0.14% by flow cytometry on week 12. Thus, he was classified as high risk, with allogeneic SCT indication in first remission. He received a 10/10 HLA-matched unrelated SCT from an ABO compatible, male, cytomegalovirus positive donor, with cyclophosphamide, total body irradiation and thymoglobulin for conditioning and cyclosporine plus methotrexatefor graft-versus-host disease prophylaxis. Prophylatic imatinib (100 mg/day) started on D+63 post-SCT. Nevertheless, molecular relapse occurred on D+170. Imatinib was replaced by dasatinib (60 mg/day) and he received three donor lymphocytes infusions (DLI), achieving molecular remission. Due to the occurrence of hematochezia and cytopenias a short suspension and subsequent dose reduction of dasatinib was necessary, after that, he tolerated well 20 mg/day for seven months. After three negative MRD, dasatinib was suspended. Ten months after dasatinib withdrawal, he had an isolated hematological relapse (51% of blasts), at two years post-SCT. He received dexamethasone and dasatinib for cytoreduction followed by IntReALL protocol with hematological remission, but MRD remained positive. Dasatinib was maintained without complications. He received two cycles of blinatumomab, achieving molecular remission. He underwent a second SCT with haploidentical donor in third complete remission. However, he developed severe hepatic venoocclusive disease (VOD) and died on D+48. **Discussion:** Several issues related to the TKI usage post-SCT for Ph+ ALL has to be elucidate. The EBMT recommendation of prophylactic imatinib use after SCT,was based on lower relapse rate and better survival reported by a retrospective study in adults patients with imatinib. More recently, a systematic review showed that both prophylactic and preemptive TKIs approaches post-SCT improved survival of patients in CR1 before transplant. Thus, the choice ofpreemptiveuse of TKIs seems to be reasonable, since is less toxic and less immunosuppressive; however, it require a more frequent MRD monitoring by flow cytometry or IgH/TCR PCR and TKIs maintenance until at least one year after MRD negativity. **Conclusion:** : Our case illustrates the efficacy of dasatinib preemptive associated with DLI in inducing molecular remission. However, it points out that, in addition to the extension of the marrow MRD monitoring period, the duration of TKI use to guarantee the persistence of molecular remission can be long, for more than one year since MRD negativity.

https://doi.org/10.1016/j.htct.2022.09.535

OPTIMIZED PROTOCOLS OF EXPANSION OF PERIPHERAL BLOOD-DERIVED δT-CELLS FOR THE ESTABLISHMENT OF AN OFF-THE-SHELF ADVANCED CELL THERAPY AGAINST CANCER

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The use of autologous T cells expressing chimeric antigen receptors (CAR) has revolutionized the treatment of hematological malignancies. However, the use of allogeneic CAR-T cells offers many advantages over autologous therapies, including the immediate availability of cryopreserved batches for infusion and the use of healthy donor cells since it is possible to obtain high amounts of fully functional cells. Moreover, this strategy also allows for the scaling up of the production of CAR-T cells resulting in cost reduction. Cells that do not express TCR $\alpha\beta$, such as gamma delta ($\gamma\delta$) T, are an alternative source to allow widespread allogeneic therapy possible. Their ability to recognize targets in an MHC-independent manner and the expression of innate immunity receptors increases the potential of using these cells in immunotherapies. Aiming to improve the effectiveness of $\gamma\delta$ T-cell-based immunotherapies against tumors, we tested various optimization strategies. The most widely used protocol for selectively expanding Vδ2T cells relies on zoledronic acid (ZOL) stimulation of PBMCs in combination with IL-2 or/and IL-15 cytokines. Here, we tested different concentrations of IL-2 (100 and 1,000 U/mL) and IL-15 (12.5 and 100 ng/mL) with 5 μM zoledronic acid. In addition, we compared cell expansion in three defined cell culture media, OpTmizer T Cell Expansion SFM, X-vivo10, and TexMACS (supplemented with 2% AB serum). A total of twenty-four different combinations of IL-2, IL-15, and media were tested in the present study.