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Long-term IL-2 therapy after transplantation of T cell depleted stem cells from alternative donors in children

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The aim of this pilot study was to evaluate the feasibility of long-term subcutaneous application of low-dose IL-2 in children with malignancies at very high risk of relapse who underwent highly T cell and B cell depleted HLA-identical (MUD) or full haplotype mismatched related hematopoetic stem cell transplantation. We studied 11 patients with acute leukemias/myelodysplastic syndrome and juvenile myelomonocytic leukemia (active disease and/or second stem cell transplantation, $n = 8$; $\geq$CR 2, $n = 2$) and relapsed or progressive Ewings sarcoma ($n = 2$) who received prophylactic IL-2 treatment for a high probability of disease recurrence after allo-HSCT. Toxicities from IL-2 were transient fever, fatigue and local inflammation. In one patient GvHD grade III with no clear association to IL-2 administration occurred. IL-2 administration was started at median day 57 (range 13–154) post-transplant for a mean duration of 28 days (range 15–250). IL-2 administration clearly increased NK cell activity. 3 of 11 patients (ALL, AML, multifocal Ewings sarcoma) survived with a follow-up of ten years. In conclusion, long-term low-dose IL-2 subcutaneous application is feasible in children due

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to a low side effect profile even after HLA mismatched transplantation and may be a strategy to prevent relapse in pediatric malignancies with extremely high risk of relapse.

Introduction

Relapse remains the major cause of death after allogeneic transplantation in children with high risk malignancies [1]. T cell mediated graft versus host disease (GvHD) has been shown to be associated with Graft versus Leukemia (GvL) Effects [2,3], but also natural killer (NK) cells and other cells may exert cytotoxic activity [4–6].

Haplo-identical stem cell transplantation has become a well-established approach in pediatric patients with malignant diseases. Because of the risk of severe GvHD a profound T and B cell depletion is required [7].

Recently consolidated findings have shown an anti-tumor effect, especially a therapeutically usable anti-leukemic effect of alloreactive natural killer (NK) cells. Furthermore, availability of the haplo-identical donor post-transplant ensures the option of adoptive transfer immunotherapy. Hereby the risk of relapse can be reduced significantly through purified alloreactive donor natural killer cell infusion [8]. Alloreactivity has been demonstrated for a wide variety of malignancies including hematologic diseases as well as solid tumors. Clinical efficacy has been most evident for myeloid malignancies. The partial resistance of some tumor dignities is most likely due to higher expression of class I HLA. Despite frequently low class I HLA expression some malignancies are not susceptible for natural killer cell lysis. Obviously, some well-known receptors for instance KIR and certainly so far undetected different inhibitory receptors prevent relevant NK cell lysis in these malignant cell clones. One may conclude that reduced NK cell alloreactivity is associated with worse overall survival since this immunotherapeutic option is ineffective, in synopsis less potent to reduce absolute tumor load and to prevent single malignant cells from expansion immunologically [9–12].

Expansion of natural killer cells can be boosted by interleukin 2 (IL-2). Natural killer cell based immunotherapy is one of the most promising treatment strategies for highly malignant and up to now incurable malignancies. Limiting step in the development of successful cellular immunotherapy are, on the one hand to find an efficient, economic and feasible method to expand appropriate amounts of NK cells and, on the other hand, to guarantee the immunological effect of the expanded cells. This means that not only the absolute effector cell count but the functionality, in this case the ability of tumor cell lysis, is not inhibited by the process of expansion [13]. Furthermore, there is good evidence that natural killer cells and T regulatory cells, which are also expanded and stimulated by the application of IL-2, mediate protection against GvHD while maintaining graft anti-tumor activity as a positive side effect [14]. Nevertheless, overall survival in some tumor entities is influenced negatively by immunmodulation through increased number of regulatory T cells [15].

Thus, we evaluated the feasibility of low-dose IL-2 application in vivo in patients with very high risk of relapse after bone marrow transplantation of completely T cell depleted stem cells from matched unrelated ($n = 2$) and mismatched related donors ($n = 9$). Further, we analyzed the effects on NK cell mediated activity in vitro by cytotoxicity assays using the standard leukemia cell line K 562.

Patients, materials and methods

Patients and donors

11 pediatric patients with refractory malignancies (leukemias, MDS and solid tumors) received peripheral stem cells from matched unrelated ($n = 2$), or full haplotype mismatched related donors ($n = 9$). The grafts were either T cell and B cell depleted or enriched for CD34 + stem cells. Since all patients had a very high risk of relapse, they were considered for long-term administration of low-dose interleukin 2 (IL-2) treatment.