Is haploidentical HSCT for leukemias a valid alternative or still a second choice?

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Abstract

Pediatric acute lymphoblastic leukemia (ALL) has cure rates of over 90% in many developed countries and the relapse rates are continuously declining over the last decades. Ostensibly, this development leaves only few patients with an indication for an allogeneic hematopoietic stem cell transplantation (HSCT). But the increasing cure rates in children is accompanied by an exponentially rising curve of treatment related morbidity and mortality. In adult ALL the development is similar, but with cure rates roughly half those seen in children. Major advances in hematopoietic stem cell transplantation (HSCT) over the last decade have substantially decreased transplant-related morbidity and mortality. A major recent development in HSCT is the exponential use of haploidentical HSCT (haplo-HSCT) based on the ubiquitously availability of the post-transplant cyclophosphamide approach for low cost. Also, T-depleted haploidentical transplantation advanced clearly, so that haploidentical HSCT needs to be considered a serious contender. Graft-versus-host disease (GVHD), both acute and chronic, remains the major post-transplant cause of substantial non-relapse morbidity and mortality, is low in haplo-HSCT. Trials increasingly show a dissociation between GvHD and graft-versus-leukemia (GvL) with comparable non-relapse mortality, overall and relapse free survival in patients treated with a haplo-HSCT. Composite outcome measures will rearrange the weight of chronic GvHD.

Haplo-HSCT is increasingly considered the potential standard of care for non-malignant but also for

malignant indications worldwide, for good reasons. In the end, the need of a cost-efficient, suitable donor will drive the popularity of this transplant modality.

Introduction

With the introduction of well-designed clinical trials and an exemplary international collaboration of the large pediatric oncology groups, disease-free (DFS) and overall survival (OS) of pediatric ALL, a futile diagnosis in the early sixties of the last century, advanced steadily. Pediatric ALL has now cure rates of over 90% in many developed countries and the relapse rates declined continuously over the last decades[1-3]. This was mostly achieved by risk-adapted, randomized clinical trials performed within major co-operative study groups using multimodal approaches of established but intense chemotherapeutic regimens. Interestingly, this success with conventional therapies left no need and delayed the introduction of molecular targeted therapies. A major step forward was the implementation of the minimal residual disease (MRD) assessment for risk stratification based treatment approaches and prognosis[4], continuously reducing the relapse rates over the last decades and leaving relapse approaches only for a highly-selected patient population. Ostensibly, this development questions the indication for an allogeneic hematopoietic stem cell transplantation (HSCT), but the price for increasing cure rates was an exponentially rising curve of treatment related morbidity and mortality. Major advances in HCT over the last decade have substantially decreased transplant-related morbidity and mortality with an expected mortality rate now being less than 15%[5].

In adult ALL the development is similar, but with cure rates roughly half those seen in children[6]. The adverse genetics of adult ALL, comorbidities and age; therefore, less aggressive adaptation of pediatric-type chemotherapy regimens and the decentralized care outside of cancer centers could all be blamed for.

Nevertheless, poor outcomes persist and require alternative therapeutic approaches. HSCT can effectively induce remission in patients with leukemia possibly by means of alternative chemotherapies[7] used during conditioning and most importantly by an immunological mechanism, called graft-versus-leukemia effect (GvL) so that HSCT from allogeneic donors has become the standard of care for high-risk patients.

The ALL-SCT-BFM-2003 trial demonstrated that the four-year event-free survival did not differ between patients with transplantations from unrelated or sibling donors (0.67±0.03 *v* 0.71±0.05; *P*= .405), with cumulative incidences of non-relapse mortality of 0.10±0.02 and 0.03±0.02 (*P*=.017) and relapse rates of 0.22±0.02 and 0.24±0.04 (*P*= .732), respectively. Interestingly, extensive chronic GvHD occurred more frequently after MSD-HSCT with a slightly better EFS but an identical OS. No significant differences in event-free survival (EFS), overall survival (OS), or non-relapse mortality (NRM) were observed between 9/10 and 10/10 matched grafts or between peripheral blood stem cells and bone marrow[8]. Consequently, HLA-matched related (MRD) and unrelated donors (MUD) are currently equivalent options in childhood ALL.

Only for 25% of patients a MSD donor and for less than 70% of the remaining patients, a suitable MUD donor or umbilical cord blood (UCB) unit can be found[9]. The probability reaches almost zero for patients from ethnic minorities[10] or a mixed ethnic background[11]. Patients from most developing countries with no proprietary donor registries reflecting their indigenous ethnicities have similar problems. In 2008, from more than 34.000 donor searches only 9.747 patients could be transplanted from a MUD[12]. Lacking a HLA-matched donor, haploidentical stem cell transplantation (haplo-HSCT) from relatives, foremost parents, is used as an alternative allograft offered to any patient with an indication for a HSCT. In the past, outcomes after transplantation with MSD or MUD donor types were far superior to the survivals with haploidentical donors, so that a haplo-SCT was a second-choice[13]. Most recently haplo-SCT, T-depleted or post-transplant cyclophosphamide (post-cyclo HSCT), advanced enormously, improving the outcomes of this transplant modality considerably. The majority of patients have a family member, identical for one HLA haplotype.

Is haploidentical HSCT for leukemias a valid alternative or still a second choice?

Haploidentical donor based HSCT dates back into the last century and was mostly experimental. Recent developments clearly improved and corrected most

drawbacks and the reputation of this in general very attractive treatment option. A pivotal development in haplo-HSCT in recent years was the post-cyclo HSCT approach which led to an exponential use of haplo-HSCT within a few years.

But is it time now to topple our standard donor selection process and to prefer a haplo-HSCT over a MSD/MUD HSCT?

Next to the almost ubiquitous availability of haploidentical family donors, immediate donor availability abrogates the need for 'bridging' therapies in malignant diseases to maintain patients in remission until graft procurement from MUD donors. Access to donor-derived cellular therapies and the possibility for a timely re-transplant can be pivotal. Also, time from collection to infusion are shorter, time to engraftment is accelerated in haplo-HSCT. The EBMT reports 1.170 HLA-identical sibling and twin transplantations in children in 2012[14], the majority presumably from minor siblings. There is increasing ethical concerns to use minors since parents are also obliged to act in the best interests of the donor sibling[15]. UK policy discussions for the protection of minor sibling donors propose to use these only if a recipient sibling will suffer from serious complications or die without the transplantation and no other medically equivalent donors are available. There is no moral or legal basis to violate the donor sibling's right to bodily integrity[16]. These ethical concerns are a breach to the silent agreement of the transplant community's algorithm to prefer MSD and ethical boards across Europe increasingly raise concerns about this approach in minors.

GvHD, both acute and chronic, remains the major post-transplant cause of substantial non-relapse morbidity and mortality[17-19]. The detrimental outcomes associated with chronic GvhD forced the need for reinterpretation of EFS and OS which were unable to fully reflect the long-lasting complications associated with transplantation complications such as extensive chronic GvHD.

GvHD-free/relapse-free survival (GRFS) is a novel composite endpoint in which events include grades 3-4 acute GvHD, chronic GvHD requiring systemic therapy, relapse, or death is censored to completely characterize survival without mortality or ongoing morbidity[20]. Thereupon, the association of chronic GvHD and global severity was taken into consideration with transplantation outcomes and showed that patients with severe but even only moderate chronic GvHD have a significantly inferior OS and worse NRM[21,22].

The low incidence of acute or chronic GvHD in 10/10 MSD is a tenacious myth. Peters et al showed in children that the incidence of extensive chronic GVHD occurred more frequently after MSD-HSCT (14% vs. 6%)[8]. In 537 adult patients the cumulative incidences of acute GvHD of grades II–IV and III–IV were 47 and 19% in patients with a sibling donor and 38 and 7% in patients with an URD (P<0.001). The cumulative 5-year incidence of chronic and severe GvHD was also higher in the sibling donor cohort (57 vs 28%, P<0.001) and (12.4 vs 2.5%, P<0.001), respectively[23]. This was attributed to a more intensive immunosuppression in MUD donors as well a higher stem cell dose in MSD, known to be associated with a high incidence of chronic GvHD[24]. Nevertheless, the OS in MSD and MUD, were almost identical in both series. This is corroborated by Kröger et al[25], who investigated in a prospective, multicenter, open label, randomized phase 3 study the role of ATG as part of conditioning on GvHD and relapse in MSD transplantations for acute leukemia. At 24 months, the cumulative incidence of chronic GvHD was 32.2% in the ATG group and 68.7% in the non-ATG group (P<0.001). The 2-year RFS were similar, 59.4% and 64.6%, respectively (P=0.21) and the OS were 74.1% and 77.9%, respectively (P=0.46). The GFRS at 2 years was significantly higher in the ATG group compared to the non-ATG group (36.6% vs. 16.8%, P=0.005). This trial elucidates that MSD are no guarantee to avoid severe chronic GvHD, secondly chronic GvHD is not a sine qua non for RFS but rather spoil the most relevant indicator of a successful HSCT, which is GFRS.

On the other hand, GvL is considered one of the backbones of a successful HSCT for hematological malignancies[26-29]. Presence of GvHD leads to a lower relapse rate compared to patients without GvHD and transplants from homozygous twin donors have a higher risk of relapse compared to MSD[30]. Therefore, the consequence for generations of transplant physicians was that there is no cure of leukemia post-HSCT without GvL, presumably to be achieved only with 'a little GvHD'- a Pandora's box for patients and physicians to keep the balance between post-

transplant GvHD and the risk of relapse.

The incidence of GvHD in T-depleted haplo-HSCT is known to be very low[31-34], but also in post-cyclo HSCT a low incidence of acute and chronic GvHD is increasingly reported[35-38]. For example, Kasamon et al[39] evaluated 271 consecutive patients with hematologic malignancies, age 50 to 75 years, who received a non-myeloablative, T-cell-replete haplo-HSCT with high-dose post-transplantation cyclophosphamide. The incidence of acute GvHD 180 days post-HSCT in 50-75 years old patients (n=271) was 3% with no chronic GvHD. Ciurea et al[40] compared the outcomes of adults with acute myeloid leukemia (AML) after haploidentical (n=192) and 8/8 HLA-matched unrelated donor (n=1.982) transplantation. The 3-month acute grade II-IV (16% vs 33%, P<0.0001) and 3-year chronic GvHD (30% vs 53%, P<0.0001) were significantly lower after haploidentical compared with matched unrelated donor transplants. The 3-year OS were 45% and 50% with haplo-HSCT and MUD transplants. McCurdy et al[41] retrospectively analyzed 684 adults with hematologic malignancies who compared different transplant modalities with post-cyclo-HSCT. They found no differences in GFRS after either myeloablative MUD or non-myeloablative HLA-haploidentical, compared with myeloablative MSD transplantations. Piemontese et al[42] compared EBMT registry data from 265 patients with acute leukemia who received a post-cyclo haplo-HSCT with 2.490 MUD and 813 mismatched MMUD (9/10). In this series HSCT from either MMUD or haploidentical donors were comparable in OS and RFS but slightly inferior to 10/10 MUD but no difference in the incidence of either acute GvHD > II or chronic GvHD according to donor type. Differences in the incidences of GvhD in the different series seem to be dependent on the stem cell source with traditionally higher incidences in PB versus BM, in analogy to what is known from MUD HSCT[24].

This discrepancy between low rates of acute and chronic GvHD and comparable rates of RFS raise the question if the GvL effect is HLA-related, immunologically specific to the leukemia or is a result of non-HLA histocompatibility antigens/innate immunological processes yet undiscovered, both or the effect of many other unknown mechanisms[43].

Will post-cyclo HSCT displace MUD transplants for malignant diseases? In Western countries, the selection process will focus on other aspects but donor availability. In countries with no donor registries and limited health-economical resources, post-cyclo HSCT is very intriguing.

T-cell depleted haplo-HSCT is costly, technically demanding and labor intensive which might limit its application to highly experienced centers. Considering the role of T-depleted haplo-HSCT, the choice for adults is easier. The diseases with a transplant indication are mostly malignant and due to the poor thymic function in adults, T-cell immune recovery depends on peripheral expansion of donor T-lymphocytes, which is limited in T-depleted grafts. The situation in children is different. Jaiswal et al[44] reported on 25 children transplanted with a post-cyclo HSCT for malignant and non-malignant diseases. The cumulative incidences of acute GvHD and chronic GvHD were 40.3% and 16.7%, respectively. On subgroup analysis, acute GvHD developed in 80% of patients <10 yr compared to only 13.3% in those between 10 and 20 yr, despite similar graft composition with significantly higher NRM (60% vs. 0%; p=0.001). This difference was attributed to an age-dependent metabolism and different immunosuppressive regimens. Whereas in adults, adverse events related to post- transplant cyclophosphamide might be limited, in children with a substantially higher risk to develop veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) a combination of a myeloablative busulfan-based conditioning followed by cyclophosphamide might raise this risk substantially[45]. Concerns that donor stem cells are exposed to the potentially mutagenic effects of cyclophosphamide post-transplant might not be true for adults[46], but with the prolonged life expectancy this might be relevant in children.

For non-malignant diseases GvL is of no use but no GvHD is a 'must' and the direct comparison between both transplant modalities might be necessary to solve the question on the incidence of GvHD with both modalities, although the trend toward a lower incidence in T-depleted haplo-HSCT is intuitive. Additionally, factors like pre-transplant immunity of the recipient, suppressed or absent in malignancy and overly active in polytransfused patients with thalassemia or sickle cell disease might modulate the post-transplant outcome. A series of 14 patients

with sickle cell disease transplanted with post-cyclo HSCT reported a graft-failure rate of 43%[47] and in another series of patients with sickle cell disease, transplanted with post-cyclo HSCT, 4 of 24 developed an uncontrollable and futile macrophage activation syndrome (personal communication, J. De la Fuente). Furthermore, the role of silent or cryptic antigenic epitopes during the in-vivo selection process is unclear. Uncovered during a 'cytokine storm' or the loss of epitopes that induce tolerance and anergy, are uncontrollable in-vivo processes that can corrupt the selection process, causing serious problems. Minor problems like the presence of antidonor HLA antibodies, mostly from parous women against paternal HLA antigens can be overcome[48].

All things considered, haploidentical HSCT is a valid alternative for leukemias in adults, the remaining entities and other age ranges need to be elucidated further.

Declaración de conflictos de interés:
El autor declara no poseer conflictos de interés.

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