



Haploidentical Hematopoietic Stem Cell Transplantation for Acute Leukemia: Early Hype or Sustained Enthusiasm

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Keywords

Haploidentical; Post-transplantation cyclophosphamide; Pediatric; GVHD

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is probably the only curative option for the majority of patients suffering from acute leukemia, either in first complete remission or after relapse [1-3]. However, the biological probability limits the availability of a matched family donor (MFD) to only a quarter of such patients. The expanding registries for volunteer unrelated donors provide a 10/10 HLA-matched unrelated donors (MUD) to 60-70% of Caucasian population but to only 10-20% of the other ethnic groups globally [4]. Unrelated Cord blood transplantation (UCBT) has conventionally allowed choice of cord units with less stringent HLA matching criteria and thus expanding the donor pool beyond the barrier of race or ethnicity. However, recent studies have highlighted the need for more stringent HLA matching for UCBT to reduce the non-relapse mortality [5]. In the midst of these conundrums, HLA-haploidentical family donor has been evolving as the alternate donor of choice for patients with acute leukemia.

The Evolution of Haploidentical HSCT

Whilst complete HLA compatibility has been at the core of developing MUD transplantation, certain groups had attempted HSCT from haploidentical family donors in the 1980s. The results were disastrous with severe early alloreactivity or graft rejection dominating the outcome and as a natural consequence, this approach took a backseat [6]. It was not until the late 90s that the world recognized the art and science of carrying out haploidentical HSCT through the pioneering work of Aversa and colleagues [7]. Earlier Reissner and Martelli had demonstrated the feasibility of HSCT across major histocompatibility barriers in mice models using high doses of purified CD34 cells [8]. It was conceptualized that if the graft contains CD 34+ cells at 'megadoses' engraftment could be possible in adequately immunobliterated patients without the risk of graft-versus-host disease (GVHD). This concept was translated to the clinic by the Perugia group over an 8 year period of rigorous research to optimize selection of CD34 cells in the graft and achieving the perfect balance of pre-transplant conditioning and graft manipulation. In a landmark study, Aversa et al reported 100% engraftment without GVHD in 43 patients with advanced leukemia with surprisingly low relapse rates in patients with acute myeloid leukemia (AML) [7]. However, the reconstitution of the immune system was significantly delayed following this approach and infection-related mortality was high.

Natural Killer Cells and Graft-Versus-Leukemia (GVL) Effect

The key to the success of allogeneic HSCT in patients with acute leukemia lies in the eradication of residual leukemia by donor derived immune system termed as GVL. Traditionally this was attributed to T lymphocytes as borne out by the documented increase in disease relapse following T cell depleted allogeneic transplants from matched sibling donors and an inverse correlation between GVHD and relapse [9].

NK cells are an integral part of the innate immune system which operates through negative feedback of inhibitory receptors based on self-recognition of corresponding ligands in the form of HLA-C and Bw4 antigens. Absence of the corresponding ligands removes the inhibitory feedback allowing the activating receptors bind to the targets and exert its cytotoxicity [10]. This effect was unearthed in the context of allogeneic HSCT by the Perugia group in the context of haploidentical HSCT where this phenomenon is operational through mismatches in HLA class I [11]. This

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Received Date: 23 Jun 2016

Accepted Date: 11 Jul 2016

Published Date: 15 Jul 2016

Citation:

Jaiswal SR, Chakrabarti S. Haploidentical Hematopoietic Stem Cell Transplantation for Acute Leukemia: Early Hype or Sustained Enthusiasm. Clin Oncol. 2016; 1: 1052.

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was termed NK cell alloreactivity and was shown to have a strong influence in reduction of relapse in patients with AML.

Exploiting NK Cell Alloreactivity

Following the concept of NK cell alloreactivity, graft manipulation evolved to exploit this phenomenon. Rather than selecting CD34 + cells, the focus shifted to depleting T and B cells in the graft to leave NK cells intact in the graft. The results were encouraging but with moderate increase in GVHD [12]. With the focus on reducing GVHD without compromising the GVL effect or the immune reconstitution, the attention shifted to removing only a dominant subtype of T cells expressing TCR $\alpha\beta$ receptors which are responsible for alloreactivity, leaving behind a small but significant population of T cells expressing $\gamma\delta$ receptors [13]. TCR $\gamma\delta$ + T cells were identified as small population of the innate immune system similar to NK cells with potent anti-tumour and anti-viral effect. Early studies employing this approach seem promising [14].

Another Shift in the Paradigm

The Johns Hopkins group explored the concept originated by George Santos several decades back that high doses of cyclophosphamide (Cy) used in the post-transplant period would reduce GVHD. In several preclinical models, Jones and Luznik demonstrated that hematopoietic stem cells (HSC) are immune from the cytotoxicity of Cy due to the inherent presence of high amounts of aldehyde dehydrogenase in these cells which inactivate the metabolites of Cy [15]. Based on these premises, O'Donnell and colleagues carried out a pilot study employing two doses of Cy at 50 mg/kg on third and fourth days after infusion of marrow graft. GVHD prophylaxis was initiated 24 hours after the second dose of Cy [16]. The initial results were spectacular with over 90% sustained engraftment with a reduced incidence of both acute and chronic GVHD. The conditioning employed was nonmyeloablative and not surprisingly, the relapse rates were high as most patients had advanced malignancies. Thus the concept of post-transplantation Cy (PTCy) reappeared from the ashes as a testimony to the brilliance of its innovator. Since the first publication in 2002, over a thousand such haploidentical HSCT has taken place worldwide [17]. Both marrow and mobilized peripheral blood and myeloablative as well as nonmyeloablative conditioning have been employed with PTCy based HSCT from haploidentical donors. The PTCy approach being less challenging both technically and financially have been globally explored and has put haploidentical family donor in the forefront of alternative donor HSCT. Over the last two decades, developments in the field of haploidentical HSCT have revealed that the outcome of either a graft manipulated or a PTCy based approach yield results similar to that of MFD or MUD [18,19].

Early Hype or Sustained Enthusiasm

Haploidentical HSCT stands at the crossroads of a paradigm shift in the field of allogeneic HSCT. Painstaking basic and clinical research has yielded the phenomenal results that we are witnessing today. Yet, these are early days and the quantum of the unknown is overbearing. This was demonstrated by a very high incidence of alloreactivity in children less than 10 years old undergoing PTCy based HSCT [20-22]. This calls for well conducted studies exposing caveats in the approaches if they exist and mending them in time. A sustained yet tempered enthusiasm might result in realizing the potential of haploidentical HSCT and resolve the reigning uncertainties in the field of alternate donor HSCT.

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