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Alternative donor transplants for severe aplastic anemia: current experience

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ABSTRACT

Patients with acquired severe aplastic anemia (SAA), who lack a human leukocyte antigen (HLA) identical sibling donor (SIB), have two therapeutic options: immunosuppressive therapy with anti-thymocyte globulin (ATG) and cyclosporine (CsA), or a transplant from an alternative donor. In these patients, the current guidelines of the European Group for Blood and Marrow Transplantation (EBMT) call for a course of ATG + CsA first and transplantation in case of no response. The alternative donor source can be an unrelated donor (UD), a cord blood (CB) unit, or a family mismatched member, in most instances genetically HLA haplo-mismatched (HAPLO). In the present review, we will discuss recent results of transplants from matched UD and SIB donors, with significantly improved outcome, especially with UD in the past decade. We will also be looking at CB transplants, and the problems of limited stem cell dose. Finally HAPLO grafts have been explored in patients lacking or having rejected an unrelated or CB graft: early results seem encouraging, though the procedure should still be considered experimental.

1. Unrelated donor transplants

1.1. The search for an alternative donor

The standard candidate for an unrelated donor (UD) transplant is a patient with acquired severe aplastic anemia (SAA), having failed one course of anti-thymocyte globulin (ATG) plus cyclosporine (CsA) [1]. However, considering the unpredictable clinical evolution after ATG + CsA, and the approximately 30% chance of non-response, the search for an UD should be initiated at diagnosis in patients under the age of 60. This implies high-resolution typing of the patient and the family: this step is relevant because it may identify a family donor who is not human leukocyte antigen (HLA) genetically identical with the patient but still suitable. Indeed, approximately 5% of family members will be either HLA phenotypically matched (at least at the A, B, C, DRB1 level) or one-antigen mismatched because of HLA antigen shared by the parents. These partially mismatched or phenotypically matched family donors will result in outcomes similar to an 8/8 matched UD: in the period 2001–2014, at the transplant Unit in Genova San Martino, we have grafted 63 patients from matched identical sibling donors (SIBs) (n = 30), UD (n = 25) cord blood (CB) (n = 2), and one-antigen family mismatched donors (n = 6); survival after UD or family mismatched grafts is quite similar (80% and 83%, respectively) [2]. Thus, 6/27 alternative donors (22%) have come from partially mismatched family members, confirming the usefulness of careful high-resolution HLA typing of patient and family at diagnosis of the disease, particularly since a family member can be rapidly prepared for donation.

1.2. HLA matching and UD transplants

An 8/8 high-resolution HLA A, B, C, DRB1 matched UD is an ideal match: the question is whether $<8/8$ is also acceptable. A Center for International Blood and Marrow Transplant Research (CIBMTR) study [3] has compared the outcome of 8/8, 7/8, and 6/8 matched UD in non-malignant disorders: the outcome of $<8/8$ matched UD transplants was significantly inferior to 8/8 matched grafts, with the major problem being graft failure. In a multicenter study in SAA patients, Deeg and coworkers also reported superior results with 8/8 matched UD as compared to $<8/8$ matched donors [4].

An European Group for Blood and Marrow Transplantation (EBMT) analysis looked at 100 patients grafted with a homogeneous conditioning regimen [5]. There were 75 unrelated transplants with full HLA typing: 46 were classified as HLA matched (reported as 8/8 or 10/10 allele matched) and 29 were mismatched, the donor being 1 or more allele mismatched with the recipient. The crude mortality of HLA matched and HLA mismatched transplants was 17% versus 34% ($P = .1$). Interestingly patients grafted within 2 years from diagnosis (n = 45) had low mortality, whether HLA matched or HLA mismatched (10% matched v 7% mismatched, $P = .7$), whereas patients grafted beyond 2 years from diagnosis (n = 30) had a higher mortality, and more so when HLA mismatched (33% v 53%, $P = .2$); the

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addition of low-dose total-body irradiation (TBI) reduced the difference in survival between matched and mismatched donors [5]. Therefore, the aim of the UD search is an 8/8 high-resolution HLA A, B, C, DRB1 matched donor; a 7/8 donor is possibly acceptable.

1.3. The conditioning regimen for UD transplants

The combination of fludarabine and cyclophosphamide (FC) seems to have gained international approval, following a number of studies [5–12]. All of these studies agree that the FC combination, initially introduced by the Houston group in the transplant arena [13], is particularly suitable for transplants in SAA, combining low toxicity with high immunosuppressive activity. With FC being the base of the conditioning for UD transplants, the question was whether the addition of low-dose TBI would be beneficial, in terms of engraftment and long-term survival. Again many studies agreed that 2–3 Gy TBI appeared to be safe and effective [5,6,14]. ATG has been part of the conditioning regimen since the early 1970s [15] and continues to be a positive predictor of survival also in the UD setting [16]. Therefore most centers are currently using either FC+ATG (FCA) or FCA-TBI low dose, for conditioning regimen in both children and adults with SAA . The dose of ATG depends on ATG brand: horse ATG (ATGAM [Pfizer, USA] is given at 40 mg/kg/d $\times 3$), rabbit ATG (thymoglobulin; Sanofi, France) is given at 2.5 mg/kg/d $\times 3$, or 3.75 mg/kg /d $\times 2$ as in Fig. 1, and rabbit ATG (Fresenius, Germany) is given at 10 mg/kg/d $\times 3$.

The original FC protocol called for cyclophosphamide (CY) 300 mg/m^2/d $\times 4$ [5]; however, in order to reduce rejection to a minimum, the current recommendation is CY 30 mg/kg/d $\times 4$. A dose de-escalation study on CY has shown that 150 mg/kg may be hazardous in these patients [17].

A standard conditioning regimen for UD transplants is shown in Fig. 1. The combination of CsA and low-dose methotrexate (MTX) has been shown to be superior to CsA alone, and is recommended.

Alemtuzumab (Campath, Sanofi, France) used with fludarabine and CY 300 mg/m^2 $\times 4$ (FCC) has recently been reported to yield encouraging results, with a very low incidence of chronic graft-versus-host disease (GvHD), and can be considered as a substitute to ATG [18]. The interesting observation is that the FCC regimen seems to be highly effective also in the absence of low-dose TBI [19]. A comparison of the FCA-TBI and the FCC regimens would be interesting, since we would like to avoid radiation in nonmalignant disorders. Some centers are still using high-dose total lymphoid irradiation (TLI) [20]; although the rate of engraftment is high and the survival very good [21], one should always be aware of the long-term effects of radiation, such as secondary malignancies, which have become evident only 10 years or more after transplant [22]. Indeed, the question is whether also low-dose TBI (2–3 Gy) will increase the rate of secondary malignancies in patients with SAA, or whether such malignancies will arise later as compared to high-dose radiation.

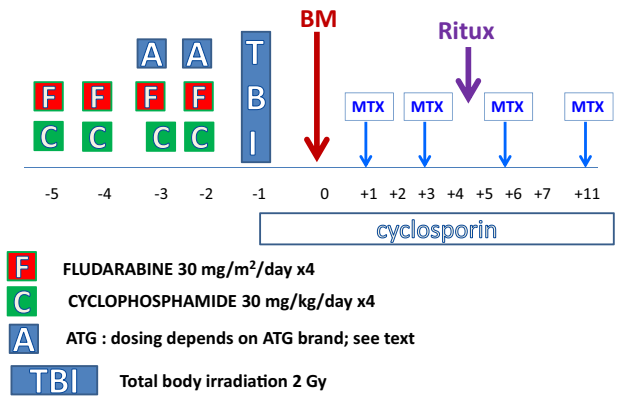

Fig. 1. Schematic rappresentation of a standard conditioning regimen for patients with acquired severe aplastic anemia (SAA) undergoing an unrelated donor transplant. MTX = methotrexate; BM = bone marrow; Ritux = rituximab 200 mg fixed dose.

1.4. Bone marrow or peripheral blood?

Several studies from the CIBMTR and EBMT have shown that bone marrow (BM) is the preferred stem cell source as compared to granulocyte colony-stimulating factor (G-CSF)–mobilized peripheral blood (PB), both in matched sibling as well as in UD transplants, in all age groups [23–25]. A very recent EBMT analysis in 1,448 cases has confirmed that, when compared to BM, PB as a stem cell source is the strongest negative predictor of survival, both for matched sibling and UD [16]; the actuarial 5-year survival is 83% for BM versus 70% for PB ($P < .00001$) (Fig. 2), and this holds true also after correcting for confounding variables. The death rate due to GvHD and infections is 7% for BM versus 17% for PB recipients ($P < .0001$). In addition, PB grafts had twice the risk of chronic GvHD as compared to BM grafts. Therefore unmanipulated bone marrow remains the stem cell source of choice in patients with acquired SAA undergoing a first allogeneic transplant, both from SIB as well as from UD. Unrelated donors should be asked to give BM and, when there are multiple donor options, then donors only willing to give PB should be rejected in favor of those willing to give BM.

1.5. How do sibling and UD transplants compare?

We have recently completed an analysis of UD versus sibling grafts performed in the period 2005–2009 [16]. We found significant more acute and chronic GvHD in UD grafts; however, survival in multivariate analysis was not different, and was influenced by other negative predictors such as the use of PB as a stem cell source, no ATG in the conditioning, older age (> 20 years), and a longer interval between diagnosis and transplant (> 6 months). The use of these four predictors allowed us to identify three risk groups; in the low-risk group (young patients, grafted early) results were overall excellent, but SIB grafts still seemed to do better than UD (91% v 81%) ($P = .05$); in the intermediate-risk group (the largest group with 468 SIBs and 336 UD), survival was superimposable (74% v 62%) and this was true also for high-risk patients (older, PB grafts, longer interval from diagnosis to transplant). Therefore, in the average SAA patient it now seems that SIB and UD produce comparable survival, although GvHD is more frequent after UD grafts.

2. Unrelated cord blood transplants

Unrelated cord blood (UCB) transplants have been recently reviewed [26]. The review includes 71 patients who received a single UCB transplant (n = 57, 80%) or double UCB (n = 14, 20%) between January 1996 and January 2009 in 32 centers. More than 50% of patients were children (median age, 13 years). Most patients (69%) received reduced-intensity conditioning regimens that were fludarabine-based. The cumulative incidence of neutrophil recovery at day 60 was 51% ± 6% with a median time of 25 days (range, 6–91). In multivariate analysis, the only factor associated with shorter time to engraftment and higher probability of engraftment was the pre-freezing total nucleated cell (TNC) dose ($> 3.9 \times 10^7$/kg) ($P < .05$). GvHD grade II–IV was seen in 20% of patients and 11/34 at risk developed chronic GVHD. The estimated probability of 3-year overall survival was 38% ± 6%. The