Stem cell transplantation - Section 17

Unmanipulated haploidentical transplantation for adult patients with hematological malignancies

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Take home messages

• The number of patients transplanted using Haplo-HSCT is increasing consistently in Europe and United States.
• Haplo-HSCT with the use of PTCy for GVHD prophylaxis, allows low incidence of grade III to IV acute GVHD, chronic GVHD, and comparable survival with HLA-matched unrelated and cord blood transplantation.

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) represents a curative treatment for different hematological disease. HSCT from a human leukocyte antigen (HLA)-matched sibling donor (MSD) is the standard of care for treating those patients, however only 25% to 30% of the patients in need have a MSD available. Even with the use of large unrelated donor registries, 25% of Caucasian patients are unable to find an HLA matched unrelated donor (MUD), and this percentage increases to 50% to 85% for individuals of other ethnicities.

Historically, the use of mismatched related donor was limited by the high level of HLA disparities, rendering this strategy such an alternative, using a “megadose of CD34+ selected graft” after ex-vivo T-cells depletion, to avoid severe graft versus host disease (GVHD). However, this approach was associated with high risk of graft failure, relapse and delayed immune recognition.

More recently, the use of novel strategies without ex-vivo T-cell depletion made the use of unmanipulated haploidentical transplants (haplo-HSCT) feasible, allowing a continuous increase in its use in different countries.

Current state of the art

Haplo HSCT are attractive because do not require any graft manipulation, and allow important reduction of costs, making the procedure affordable for the majority of transplant centers. In addition, family donors are easily available and highly motivated, the procedure may be organized fast, avoiding delay. There are several platforms of haplo-HSCT available, and among them, two main approaches were developed in the last decades with different platform of GVHD prophylaxis, based either on anti-thymocyte globulin (ATG) or on post-transplant cyclophosphamide (PT-Cy). Details on the recent studies available are showed in Table 1.

ATG allows extensive in vivo T-cell depletion and induces tolerance with expansion of regulatory T-cells. ATG effectively reduce GVHD incidence after both MSD and MUD HSCT. The Beijing group first reported the efficacy of the “GIAC protocol” in haplo-HSCT, using intensified immunosuppression through ATG, cyclosporine (CSA), mycophenolate-mofetil (MMF), short-course methotrexate, and monoclonal antibodies. On the other hand, Luznik et al introduced the use of high dose PT-Cy for GVHD prophylaxis in the combination with reduced-intensity conditioning regimen (RIC) and bone marrow (BM) as stem-cell source. In the absence of prospective trials comparing the different platforms of haplo-HSCT, most of the data come from single centers or registries reports.

The PT-Cy is more frequently associated with calcineurin inhibitors and MMF, however some authors reported the efficacy of the PT-Cy in combination with rapamycin to enhance regulatory T-cells, showing low rates of acute GVHD and NRM, and favorable immune reconstitution profile.

Despite the low incidence of acute and chronic GVHD and the low NRM also for older patients reported with RIC PT-Cy, disease recurrence is rather high, partially due to the high risk disease in most of the transplanted patients.

The broad HLA disparities in the haplo setting was a limitation to the use of peripheral blood stem cell (PBSC). With the intent to
Ruggeri and Santoro

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| Author, Journal | Year | Disease (%) | BM/ PBSC | Disease (%) | BM/ PBSC | Disease (%) | BM/ PBSC | Disease (%) | BM/ PBSC | Disease (%) | BM/ PBSC | Disease (%) | BM/ PBSC |
|----------------|------|-------------|----------|-------------|----------|-------------|----------|-------------|----------|-------------|----------|-------------|----------|
|  | | | | | | | | | | | | | |
| Martelli et al. Blood 2014 | 2014 | 43 | AML 77% ALL23% | CR1 58% | 3.8 | TCD PBSC | 40 | 95% | 15% | NA | 2.4% | 4.9% | 40% | 1.5y | 56% | NA |
| Ciceri et al. Blood 2008 | 2008 | 173 | AML 65% CR1 29% | 3.9 | MAC TCD PBSC | 37 | 91% | 100 d5% | NA | 2 y | 10% | 2 y | 16% | 2 y | 48% | NA |
| 93 | ALL 35% 39% | 2.4 | MAC TCD PBSC | 21 | 91% | 100 d18% | NA | 2 y | 19% | 2 y | 26% | 2 y | 44% | 2 y | 13% | NA |
| Di Bartolomeo et al. Blood 2013 | 2013 | 80 | AML 56% | 56% | 1.5 | MAC BM 37 | 93% | 100 d24% | 5% | 2 y | 17% | 1 y | 21% | 1 y | 36% | 3 y | 44% |
| Ciurea et al. Blood 2015 | 2015 | NM 88 | AML 100% | 82% | 3.3 | NS PTCy BM 88% | 88% | 90% | 3 m | 16% | 3 m | 7% | 3 y | 30% | 3 y | 44% | 3 y | 14% | N/A | 3 y | 45% |
| McCurdy et al. Blood 2015 | 2015 | 372 | AL 31% | MDS/MPN 9% | 84% | 4.1 | NS PTCy BM 55 | 92% | 3 m | 32% | 3 m | 4% | 2 y | 13% | 3 y | 46% | 3 m | 8% | 3 y | 40% | 3 y | 50% |
| Kasamon et al. JCO 2015 | 2015 | 271 | AML 24%, MDS 13%, ALL 3% | 84% | 4 | NS PTCy BM 61 | 94% | 6 m | 33% | 6 m | 3% | 1 y | 10% | 2 y | 52% | 6 m | 8% | 3 y | | |
| Cancer 2016 | 2016 | 60 | AML/MDS 67%, ALL 12% | 67% | 2 | NS PTCy BM 45 | 97% | 100 d 28% | 100 d | 3% | 2 y | 24% | 2 y | 24% | 2 y | 23% | 2 y | 53% | 2 y | 55% | |
| Santoro et al. JHO 2017 | 2017 | 208 | ALL 100% | CR1 44% | 2.5 | NS BM 57% 53% | 32 | 92% | 100 d 31% | 100 d | 11% | 3 y | 29% | 3 y | 37% | 3y | 32% | 3 y | 31% | 3 y | 33% | |
| Bashey et al. JCO 2017 | 2017 | BM 481 | AML 39%, ALL 14% | 63% | 2.9 | NS BM 58 | 91% | 6 m | 25% | 6 m | 7% | 2 y | 20% | 2 y | 45% | 2 y | 17% | 2 y | 41% | 2 y | 54% | |
| Ruggeri et al. Cancer 2018 | 2018 | BM 260 | AML 75% | CR1 67% | 1.8 | MAC BM 46 | 92% | 100 d 22% | 100 d | 4% | 2y | 36% | 2y | 27% | 2y | 23% | 2y | 23% | 2y | 49% | 2y | 55% | |
| PB 191 | AML 71% | 1.5 | MAC BM 44 | 95% | 100 d 38% | 100 d | 14% | 2y | 32% | 2y | 22% | 2y | 54% | 2y | 17% | 2y | 41% | 2y | 54% | |
| Santoro et al. Cancer 2019 | 2019 | MAC 373 | AML 100% | CR 1 48% | 2.5 | MAC BM 54% 53% | 55 | 91% | 100 d 25% | 100 d | 8% | 100 d 27% | 2 y | 25% | 2 y | 31% | 2 y | 44% | 2 y | 48% | |

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