

## Unrelated cord blood transplantation and post-transplant cyclophosphamide

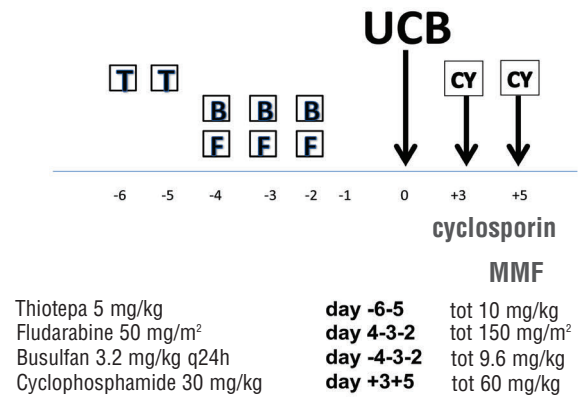
The number of unrelated cord blood transplants (UCBT) are declining in Europe,<sup>1</sup> despite comparable outcome with grafts using unrelated donor peripheral blood or bone marrow.<sup>2</sup> The reasons for the decline may be due to the well-known slow engraftment and delayed immune reconstitution of UCBT, which may result in a significant risk of infections and non-relapse mortality (NRM).<sup>3,4</sup>

Neutrophil and platelet recovery can be shortened by direct intra-bone injection of CB cells,<sup>5</sup> but immune recovery remains an issue, especially when anti-thymocyte globulin (ATG) is used in the conditioning regimen.<sup>5</sup> In the absence of ATG, grade III-IV acute graft versus host disease (GvHD) is reported to be 21%,<sup>6</sup> and when ATG is added in the transplant platform, GvHD is reduced (15%),<sup>6</sup> but immune reconstitution is delayed, leading to infectious complications, and late viral infections.<sup>4,7,8</sup> The crucial role of ATG and the risk of over or under exposure is further proven by the attempt to optimize ATG dose based on lymphocyte counts, rather than patient's weight,<sup>9</sup> and by carefully assessing the speed of CD4 recovery according to ATG dosing pre-transplant.<sup>10</sup> An additional reason for the decline in numbers of UCBT is the competition of HLA haploidentical transplants (HAPLO),<sup>11</sup> especially performed with post-transplant cyclophosphamide (PT-CY), as first described by the Baltimore group.<sup>12</sup> We have been particularly impressed with the speed of immune recovery of HAPLO transplants with PT-CY,<sup>13</sup> with median CD4 counts on day +100 (190/ $\mu$ l) comparable to CD4 counts after HLA identical sibling grafts (229/ $\mu$ l), and significantly higher as compared to unrelated and cord blood grafts receiving ATG for GvHD prophylaxis.<sup>13</sup>

We therefore hypothesized that PT-CY would be an effective GvHD prophylaxis regimen for patients undergoing an UCBT and, by preventing GvHD in the absence of ATG, hematologic and immune recovery could be accelerated, as seen in the HAPLO setting. We are now reporting a first case.

The patient, a 42-year-old female, was diagnosed with acute myeloid leukemia (AML) NPM1<sup>+</sup> in December 2015 with normal cytogenetics; she was induced and achieved a complete hematologic and NPM1 negative remission. The patient relapsed in June 2017 and was re-induced to a complete remission with anthracycline and cytosine arabinoside. A 5/6 UCB unit was identified with a cell count of  $4.2 \times 10^7$ /kg. On high resolution, the UCB unit and the patient were mismatched at the A locus (24:03 vs. 24:02), at the B locus (18:01 vs. 38:01), and they were DRB1 allelic matched. There was a gender mismatch (M  $\rightarrow$  F) and ABO mismatch (B+  $\rightarrow$  O+). In November 2017, she was prepared with a conditioning regimen including thiotepa 5 mg/kg on days -6 and -5, fludarabine 50 mg/m<sup>2</sup> on days -4-3-2 and intravenous busulfan 3.2 mg/kg on days -4-3-2 (Figure 1). On 14.11.2017 she received a single UCB unit. GvHD prophylaxis consisted of intravenous cyclosporine (CsA) 3 mg/kg starting on day 0, mycophenolate (MMF) 2 gr/day starting on day +1, and PT-CY 30 mg/kg on days +3 and +5. CsA was switched to oral administration on day +20.

Hematologic recovery: the patient achieved a neutrophil count of  $0.5 \times 10^9$ /L on day +15 and a platelet count of  $20 \times 10^9$ /L on day 21; platelet counts were 73 and 179 on days +50 and +100, respectively (Figure 2); chimerism was full donor, by FISH (Y probe) and



**Figure 1** Conditioning regimen and GvHD prophylaxis. T: thiotepa; B: busulfan; F: fludarabine; CY: cyclophosphamide; MMF: mycophenolate; cyclophosphamide (CY) is given on day +3 and +5 (30 mg/kg) and cyclosporine is started on day 0, and mycophenolate on day +1.

microsatellites, from the first evaluation on day +30 (Figure 2). ABO blood group conversion was complete by day +100. The patient was discharged on day +25, then readmitted on day +32 for 6 days due to fever and a flu. She has not since been readmitted to hospital. Grade I skin GvHD developed on day +20 and was not treated.

Immune recovery: there was a rapid increase of NK cells up to 326/ $\mu$ l on day +29, followed by a decline of NK cells and a rise in CD3<sup>+</sup> cells. Absolute CD4 and CD8 counts on days +50, +100 and +180 were 63 and 96/ $\mu$ l, 92 and 98/ $\mu$ l, and 150 and 220/ $\mu$ l, respectively. Her current counts on day +302 are CD4 885/ $\mu$ l, CD8 1115/ $\mu$ l and NK 575/ $\mu$ l. The patient is alive and well, NPM1 negative 10 months post UCB.

Hematologic recovery has been a long-standing issue of CB transplants. In a conventional CB transplant, with or without ATG, the median neutrophil and platelet recovery is 24 and 58 days, respectively.<sup>14</sup> Similarly, neutrophil recovery is reported to occur on day 23 and 21 for single and double CB transplants, with platelet recovery occurring on day 58 and 85.<sup>15</sup> Intra-bone infusion of CB cells has been shown to accelerate platelet recovery in one report (day 36)<sup>5</sup> and neutrophil recovery in another report (day 15)<sup>16</sup>; in the latter, however, platelet recovery remains at a median of 45 days.<sup>16</sup> Expansion of CB units is another strategy studied to improve hematologic and immune recovery: with the infusion of two CB units, one of which *ex vivo* expanded, the neutrophil recovery is accelerated to day 15, but platelet recovery remains at day 33.<sup>17</sup> The present case compares favorably with these data with a rapid recovery of both neutrophils (day +15) and platelets (day +21).

Immune recovery is the other crucial issue: Admiral and coworkers have shown that the probability of T-cell recovery (>50 CD4<sup>+</sup> T cells/ $\mu$ l within 100 days) was decreased even in the lowest ATG exposure group after unrelated CB transplant, while only the highest ATG exposure group after BM/PB grafts had poor T-cell recovery.<sup>18</sup> This patient clearly met the criteria for rapid CD4 recovery (>50 CD4<sup>+</sup> T cells/ $\mu$ l within day 100), and the lack of viral infections would confirm the strength of immune reconstitution. However, more patients will be needed to confirm this result.

In conclusion, this first patient suggests that UCB transplantation can be performed, following a myeloablative conditioning regimen, with CsA, MMF and PT-CY

for GvHD prophylaxis. Hematologic recovery as well as immune reconstitution were both fast, with no infectious complications, and no GvHD. A prospective trial has been activated to assess whether this encouraging first case can be confirmed.

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## Platelet recovery after UCB TX with PTCY

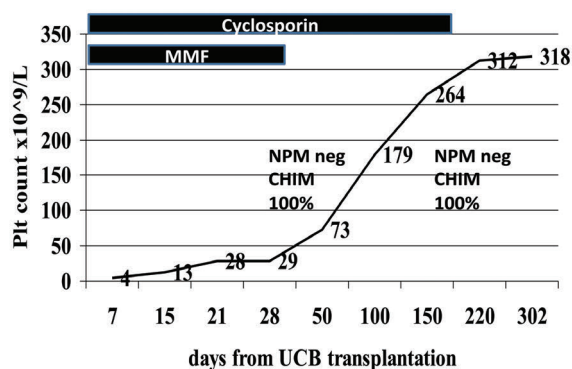


Figure 2. Platelet recovery in this patient, duration of GvHD prophylaxis and timing of full donor chimerism and NPM1 negativity.

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