Correspondence


Allogeneic transplantation of CCR5-deficient progenitor cells in a patient with HIV infection: an update after 3 years and the search for patient no. 2

In February 2007, the medical team of the Charité Berlin performed an allogeneic haematopoietic stem cell transplantation (HSCT) in an HIV-infected patient with acute myeloid leukaemia (AML) using progenitor cells from a donor, especially selected for homozygosity for the CCR5-delta32 deletion (HIV-resistance gene) [1]. Now, more than 3 years after this treatment, the patient is still off antiretroviral medication and without any evidence of viral replication. Furthermore, the patient’s CD4 cell count rose to more than 800/μl and all investigated haematopoietic stem cell derivatives, including macrophages of the gut, became CCR5 negative. This case has inspired new hopes that some kind of gene therapy may become the key to an improvement in HIV treatment and hopefully an HIV cure. Nevertheless, it was just a single case and repeating this approach in a small series of patients would be desirable to make further conclusions. Here, we report our efforts to find a second candidate for allogeneic CCR5-delta32 transplantation and the limitations of this undertaking.

The main indication for allogeneic HSCT in adults is the diagnosis of AML. In the last decade, about 3500 new cases of AML have been reported in Germany per year (incidence 3.0–3.9/100 000/year) [2]. Taking into account that only one third of these patients are less than 60 years of age and therefore eligible for allogeneic HSCT, furthermore, that a reasonable proportion of patients pass away before transplantation and, finally, that a human leukocyte antigen (HLA)-matching sibling can be found in 20%, the incidence of appropriate candidates for allogeneic HSCT could be assumed as being approximately 1.0–1.5/100 000 per year. The prevalence of HIV in Germany is about 0.0006% [3]. Taken together, in Germany, we expect to find only 0.5–1.5 patients per year with a coincidence of HIV and AML suitable for transplantation with CCR5-delta32 screened stem cells.

Currently, 75% of patients requiring an allogeneic HSCT will find at least one HLA-matched donor. The prevalence of CCR5-delta32 homozygotes in Europe is between 1% and 3%. Therefore, the likelihood of finding an HLA-matched donor is dramatically reduced if we cannot expand the donor pool by a factor of at least 10, requiring the worldwide cooperation of stem cell registries.

In spring 2009, our institution organized an international workshop bringing together leading European stem cell registries for a discussion of the possibilities and limitations of a CCR5-based donor screening [4]. The meeting came to the agreement of supporting further attempts to use CCR5-delta32 deleted stem cells in appropriate candidates. To expand the repertoire of donors, prescreened stem cells will be provided by Stemcyte, a company that already charged over 10 000 units of CCR5-tested cord blood units [5].

Since the publication of our report, we received several requests from other institutions concerning the possibility of finding CCR5-depleted donors for transplantation in HIV-infected patients with an indication for allogeneic HSCT. Table 1 shows all performed and planned CCR5 genotyping.

Table 1. Summary of CCR5 genotyping.

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Location</th>
<th>Donors CCR5 tested</th>
<th>Registered donors</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>40</td>
<td>AML</td>
<td>Berlin, Germany</td>
<td>(+, +) 52</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>Adult</td>
<td>NHL</td>
<td>Freiburg, Germany</td>
<td>(&gt;1, ND)</td>
<td>Died before Tx</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>3</td>
<td>DBA</td>
<td>Heidelberg, Germany</td>
<td>120 +*</td>
<td>103</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>Adult</td>
<td>MDS</td>
<td>Lausanne, Switzerland</td>
<td>1</td>
<td>1</td>
<td>Tx July 2010</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>29</td>
<td>NHL</td>
<td>Mann, Germany</td>
<td>1</td>
<td>1</td>
<td>Tx Nov 2009 with (+, +)</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>15</td>
<td>leukaemia</td>
<td>Jerusalem, Israel</td>
<td>3 +3*</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>30</td>
<td>CMML</td>
<td>Berlin, Germany</td>
<td>60</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>Adult</td>
<td>NHL</td>
<td>Mannheim, Germany</td>
<td>Stopped</td>
<td>Tx cancelled</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Male</td>
<td>14</td>
<td>KS</td>
<td>Dublin, Ireland</td>
<td>Pending</td>
<td>Ongoing</td>
<td></td>
</tr>
</tbody>
</table>

Proposed and performed CCR5 donor genotyping of appropriate stem cell donors for patients with HIV infection and indication for allogeneic stem cell transplantation in order of the requests. The results for CCR5 genotyping are displayed as (+, +) for wild-type, (+, –) and (–, –) for CCR5-delta32 heterozygosity and homozygosity, respectively. AML, acute myeloid leukaemia; CMML, chronic monomycelocytic leukaemia; DBA, Diamond–Blackfan anaemia; KS, Kaposi’s sarcoma; MDS, myelodysplastic syndrome; NHL, non-Hodgkin’s lymphoma; Tx, allogeneic transplantation.

*CCR5 prescreened cord blood units with 3/6 human leukocyte antigen matches.
donor screening activities carried out by our workgroup. As expected, one limitation in finding appropriate candidates was that, frequently, only few HLA-matched donors were available. Furthermore, statistically, we should have found at least one CCR5-delta32 homozygous donor in patient 3; however, the search was unsuccessful.

Several strategies have already emerged from our current understanding of persistent HIV infection and, in 1988, David Baltimore, Nobel Laureate, suggested that gene therapy could provide a possible HIV/AIDS treatment. Furthermore, techniques of gene delivery and gene knockdown have been progressed considerably today as instruments for future HIV treatment strategies. Our report, from a successful way of a ‘natural’ kind of HIV gene therapy, has kindled discussion about whether this patient is sterilizing cured [6,7]. This can be assumed more and more given the fact that, meanwhile, all infectable targets and reservoir elements have been replaced by a new generation of cells with CCR5-negative status. However, in our opinion, an important additional proof-of-concept would be that we were able to reproduce this approach in other patients.

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HBV and lymphoma: HIV matters

A recent article by Engels et al. [1] published in the Lancet Oncology concludes that persons with hepatitis B virus (HBV) are at greater risk of developing non-Hodgkin lymphoma (NHL) compared to HBV-negative individuals. However, they have failed to account for their cohort’s HIV status [1]. Patients with HIV/AIDS are up to 100 times more likely to develop NHL probably because of oncogenic viruses and excessive stimulation of B cells by HIV [2]. Despite a decrease of NHL incidence in the post-HAART era as antiretrovirals suppress B-cell stimulation, NHL remains the second commonest tumour associated with HIV-1 [3,4]. Furthermore, as many as 10% of HIV-positive patients are co-infected with HBV, in most cases due to overlapping routes of transmission [5].

To investigate the relationship between HIV, HBV and NHL further, we analysed data from 464 patients with an HIV-positive status who developed lymphoma. Of these, 5.3% of patients with Burkitt lymphoma, 7.1% of patients with diffuse large B-cell lymphoma, and 11.7% of patients with Hodgkin disease were HBV surface antigen positive ever during follow-up. Although a higher incidence of HBV in NHL patients could suggest that HBV plays a role in lymphomagenesis, it is impossible to generate this conclusion when HIV could be a confounding variable. Therefore, we analysed 555 individuals co-infected with HBV and HIV who were followed for a total of 3098 patient-years (calculated from the time they were HBV surface antigen positive to the last clinic date or date they developed NHL, whichever was sooner). Twelve patients presented with NHL at baseline and were thus excluded from our analysis, although HBV could have contributed. Eight patients (1.4%, incidence: 25.8/10,000 patient-years) developed NHL during follow-up and four patients developed Hodgkin lymphoma (0.72%, unadjusted incidence ratio 12.9/10,000 patient-years). Of these eight patients with NHL, four were diagnosed with large B-cell lymphoma and two with Burkitt lymphoma. Our patients were more than 10 times more likely to develop NHL than those in the Korean cohort. In a previous study, we followed 5832 HIV-positive patients for 34,133 person-years, during which 102 developed NHL (1.7%, incidence: 29.9/10,000 person-years) regardless of HBV status [6]. Combined, these data strongly suggest that HBV positivity does not put patients with HIV at a greater risk for NHL (unadjusted rate ratio: 0.86, 95% CI 0.64–1.09).
Our results agree with a previously published Swiss study that also found that HBV and HIV co-infection did not increase a patient’s risk of NHL compared to HIV infection alone [7]. Because HIV is associated with higher rates of HBV infection and HIV-positive increases incidence rate of NHL, this accounts for our over all higher incidence rates of NHL compared to the South Korean study. Engels et al. cannot conclude that HBV-positive persons are at higher risk for NHL without first eliminating the possibility that the increased risk is due to a sub-population of HBV-positive patients co-infected with HIV (a point that most reviewers of the paper made).

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