Role of polyomavirus in emerging secondary hypofunction of marrow graft following allogeneic bone marrow transplantation in adults

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Background

Poor function of haematopoietic transplant is considered an important complication following allogeneic bone marrow transplantation (allo-HSCT). According to different reports, incidence of BK polyomavirus (BKV) reactivation following allo-HSCT can be as high as 33-54% (1). Relation between BK viruria (or viremia) and the risk of hemorrhagic cystitis is well studied in HSCT patients (1-3). Cases of BKV-associated encephalitis and pneumonitis have been also reported (2). Some studies suggest correlation between BK virus reactivation and cytopenia in both renal (1) and bone marrow transplant recipients (2-4). Taking into account susceptibility of different cell types to BKV infection, including peripheral leukocytes (4), one may suggest a clinical form of BKV disease manifesting as bone marrow transplant insufficiency.

Objective

The aim of our study was to assess a role of BKV infection in the development of secondary graft hypofunction following allogeneic HSCT.

Materials and methods

We carried out a retrospective analysis of 328 patients with different oncohematological disorders (18 to 77 y.o., a median of 31 years), who underwent allogeneic HSCT (matched related donors, 89; matched unrelated donors, 211; haploidentical donors, 28) during the period from 2014 to 2016. Myeloablative conditioning regimen was applied in 75 patients (23% of total), reduced-intensity regimens were used in 253 cases (77% of total). Reduced-intensity regimens were used in 253 cases (77% of total). Characteristics of the group are shown in Table 1.

Table 1. Clinical characteristics of the group under study (n=328)

<table>
<thead>
<tr>
<th>Type of donors</th>
<th>MUD</th>
<th>MRD</th>
<th>Haplo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>211</td>
<td>89</td>
<td>28</td>
</tr>
<tr>
<td>Observation terms, days (median+range)</td>
<td>147 (6-729)</td>
<td>207 (2-802)</td>
<td>46 (8-599)</td>
</tr>
<tr>
<td>Active malignant process at HSCT, % of total</td>
<td>63 (30%)</td>
<td>28 (31%)</td>
<td>11 (39%)</td>
</tr>
<tr>
<td>Age at transplant, years (median+range)</td>
<td>33 (18-70)</td>
<td>31 (18-59)</td>
<td>25 (18 – 58)</td>
</tr>
<tr>
<td>Gender, females</td>
<td>99 (47%)</td>
<td>38 (43%)</td>
<td>10 (35%)</td>
</tr>
<tr>
<td>Primary diagnosis: AML</td>
<td>96 (45%)</td>
<td>34 (38%)</td>
<td>15 (54%)</td>
</tr>
<tr>
<td>ALL</td>
<td>49 (23%)</td>
<td>19 (21%)</td>
<td>5 (18%)</td>
</tr>
</tbody>
</table>
Over the posttransplant period 219 patients were tested for BKV in different body fluids including blood plasma, urine, bone marrow aspirates, CSF etc. (Fig.1), using qualitative gene-specific PCR. BKV testing was carried out both in cases of local clinical symptoms (cystitis, encephalitis, graft failure etc.), and as a routine screening. Tests were positive in 166 (78%) cases and negative in 45 patients (2%). Altered graft functioning was evaluated as follows: primary graft failure (PGF) was identified in absence of donor hematopoiesis without clinical relapse; secondary graft hypofunction (SGH) was determined as post-engraftment cytopenia with sustained donor chimerism, or as a persisting dependence on transfusions and CSF injections with full donor chimerism and no signs of tumor relapse.

### Results

Poor graft function was observed in 194 patients (59% of total); primary graft failure (PGF) was documented in 21 cases (6.4%); secondary graft hypofunction (SGH) was revealed in 172 patients (52.4%). BKV reactivation was found in 163 patients, including 42 cases with normally functioning graft, primary graft failure was diagnosed in 10 cases, whereas 111 patients exhibited SGH. BKV detection in bone marrow was a risk factor for SGH, as shown by a single-factor analysis. In the patients with BKV reactivation (n=163), PGF and SGH frequency was respectively 6.8% (n=11) and 68% (n=112). Among patients without BKV reactivation (n=56), PGF was reported in 1.7% (n=1), and SGH, in 46.4% (n=26, p<0.002), as shown in Fig.2. In SGH cases, the median time for BKV detection was 46 days, thus preceding the onset of graft hypofunction (a median of 52 days).

<table>
<thead>
<tr>
<th>Type of donors</th>
<th>MUD</th>
<th>MRD</th>
<th>Haplo</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS</td>
<td>12  (5,7%)</td>
<td>4  (4,5%)</td>
<td>1  (3,5%)</td>
</tr>
<tr>
<td>CML</td>
<td>17  (8%)</td>
<td>10  (11%)</td>
<td>2  (7%)</td>
</tr>
<tr>
<td>Lymphomas</td>
<td>19  (9%)</td>
<td>10  (11%)</td>
<td>3  (10,5%)</td>
</tr>
<tr>
<td>Myeloproliferative disease</td>
<td>10  (4,7%)</td>
<td>1  (1,1%)</td>
<td>-</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>5   (2,3%)</td>
<td>11  (12%)</td>
<td>2  (7%)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>3   (1,4%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CLL</td>
<td>-</td>
<td>3  (3,4%)</td>
<td>-</td>
</tr>
<tr>
<td>Conditioning regimen</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Myeloablative</td>
<td>50  (24%)</td>
<td>21  (24%)</td>
<td>4  (14%)</td>
</tr>
<tr>
<td>Reduced-intensity</td>
<td>161 (76%)</td>
<td>68  (76%)</td>
<td>24  (86%)</td>
</tr>
</tbody>
</table>

Fig. 1. Distribution of clinical samples tested for polyomavirus

Fig. 2. Prevalence of BK virus in primary graft failure (PGF) and secondary graft hypofunction (SGH).
BKV reactivation episodes were observed within 14 days before the onset, or during graft hypo functioning in 74 patients (43% of the SGH group, or 22.5% of the total HSCT cohort). Meanwhile, bone marrow samples were positive for BKV in 46 patients, i.e., 27% of all SGH cases, or 14% of total allo-HSCT cohort. However, BKV reactivation (including bone marrow affection) did not correlate with total survival after HSCT.

Conclusion

Post-transplant BKV infection may be a predisposing or triggering factor in the development of hematopoietic graft hypofunction. Further studies are required in order to obtain more detailed information about BKV replication in bone marrow and its potential effects upon post-HSCT survival.

References

4. Dropulic LK, Jones RJ. Polyomavirus BK infection in blood and marrow transplant recipients. Bone Marrow Transplantation 2008; 41:11–18

Keywords

Allogeneic hematopoietic stem cell transplantation, BK polyomavirus, reactivation, graft insufficiency.

Role of BK-Polyomavirus Infection in Development of Secondary Hypofunction of the Transplant Bone Marrow after Allogeneic Transplantation of Bone Marrow in Adults


NII Pediatric Oncology, Hematology and Transplantology named after R.M. Gorbachev, First Saint-Petersburg State Medical University named after acad. I.P. Pavlova

Introduction

Graft insufficiency (GI) remains one of the important problems in the development of allogeneic transplantation of the peripheral blood bone marrow (PB-TK). The frequency of BKV reactivation after allogeneic transplantation was 33-54% (1). BKV reactivation is often associated with graft dysfunction. BKV replication is widespread, and BKV infection is associated with various diseases (2). BKV replication is widespread, and BKV infection is associated with various diseases. BKV replication is widespread, and BKV infection is associated with various diseases. BKV replication is widespread, and BKV infection is associated with various diseases.

Conclusion

BKV reactivation may be a predisposing or triggering factor in the development of platelet and white cell count (WBC) hypofunction. Further studies are needed to obtain more detailed information about BKV replication in bone marrow and its potential effects after HSCT.

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Role of BK-polyomavirus infection in the development of secondary hypofunction of the transplant bone marrow after allogeneic transplantation of bone marrow in adults


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Transplantation of bone marrow (BM) remains one of the important problems in the development of graft insufficiency (GI) after allogeneic transplantation. BM transplantation (BM-TK) is associated with various diseases (1). BKV reactivation is often associated with graft dysfunction. BKV replication is widespread, and BKV infection is associated with various diseases (2). BKV replication is widespread, and BKV infection is associated with various diseases. BKV replication is widespread, and BKV infection is associated with various diseases. BKV replication is widespread, and BKV infection is associated with various diseases.

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стика пациентов приведена в Табл. 1. У 219 пациентов в посттрансплантационном периоде проводилось тестирование ВК-вирусной инфекции (ВК) в различных биологических жидкостях (моча, ликвор, плазма крови, аспират костного мозга), как показано на рис.1. Диагностика полимавирусов проводилась с помощью качественной геноспецифической ПЦР ДНК. Тестирование ВК-вируса выполнялось как при наличии клинических симптомов (цистит, энцефалит, недостаточность функции трансплантата), так и в качестве скрининга. Результаты тестирования были положительными в 166 (78%) случаях, отрицательными в 45 (2%) случаях. Производилась оценка функции трансплантата после ТГСК. В частности, под первичным неприживлением понималось отсутствие донорского гемопоэза без признаков основного заболевания; вторичной гипофункцией считалось возникновение цитопении после приживления и периода нормальной функции трансплантата при сохранении донорского химеризма или сохранявшейся зависимости от трансфузий и введения КСФ при полном донорском химеризме и отсутствии признаков основного заболевания.

Результаты

Гипофункция трансплантата наблюдалась у 193 пациентов (59%): первичное неприживление – у 21 (6,4%), вторичная гипофункция трансплантата (ВГТ) – у 172 больных (52,4%). Реактивация ВК-вируса была обнаружена у 163 пациентов, из них 42 пациентов имели нормальную функцию трансплантата, 10 – первичное неприживление, 111 – вторичную гипофункцию. Обнаружение ВК-вируса в костном мозге было фактором риска развития вторичной гипофункции трансплантата при однофакторном анализе. У больных с реакцией ВК-вируса (n=163) частота первичного неприживления и ВГТ составила 6,8% (n=11) и 68% (n=112) соответственно, тогда как у пациентов без реактивации ВК-вируса (n=56) первичное неприживление было документировано в 1,7% (n=1), а ВГТ – в 46,4% случаев (n=26, p<0,002). Эпизоды реактивации ВК-вируса имели место в течение 14 дней до развития или в период гипофункции трансплантата у 74 пациентов (43% от всех пациентов с вторичной гипофункцией, 22,5% от всех аллоТКМ). При этом в костном мозге ВК-полимавирус обнаруживался у 46 пациентов (27% от всех пациентов с вторичной гипофункцией, 14 % от всех аллоТКМ). Обнаружение ВК-вируса (при медиане сроков выявления 46 сут.) предшествовало дебюту гипофункции трансплантата (медиана появления – 52 дня).

Однако в данном исследовании реактивация ВК-вируса (в том числе и в костном мозге) не коррелировала с общей выживаемостью после аллоТКМ.

Выводы

Развитие ВК-вирусной инфекции в посттрансплантационном периоде может являться предрасполагающим или пусковым фактором для формирования гипофункции трансплантата костного мозга. Дальнейшие исследования необходимы для более детального изучения возможности репликации ВК-полимавируса в костном мозге и его влияния на выживаемость после аллоТКМ.

Ключевые слова

Аллогенная трансплантация гемопоэтических стволовых клеток, ВК-полимавирус, реактивация, недостаточность трансплантата.