Intravenous immunoglobulin G treatment of hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation


Raisa Gorbacheva Memorial Research Institute of Pediatric Oncology, Hematology and Transplantation, Pavlov University, St. Petersburg, Russia

Summary

Hemorrhagic cystitis (HC) is a frequent complication in allogeneic hematopoietic stem cell transplantation (allo-HSCT). Human BK-polyomavirus (BKPyV) may be one of the main agents found in late HC developing after allo-HSCT. In previous studies, intravenous immunoglobulin (IVIG) preparations were shown to neutralize BKPyV in mice cell cultures and to reduce BK virus nephropathy in kidney transplantation. The aim of current study was to evaluate efficiency of HC treatment with IVIG in allo-HSCT recipients, with respect to conditioning regimen intensity and presence of graft-versus-host disease (GvHD).

Patients and methods

A total of 1037 allo-HSCT recipients transplanted in R. M. Gorbacheva Memorial institute for Pediatric Oncology, Hematology and Transplantation in 2013-2018 were included into retrospective open single-center cohort study. HC was registered in 118 (11.4%) cases. According to inclusion criteria, only 90 patients were enrolled to the final analysis. This cohort was divided into two groups based on HC therapy used: the intervention group (n=42) included patients with standard HC treatment with addition of IVIG; the control group (n=48) – with standard HC therapy only.

Results

The median HC duration in common group (IVIG and control) was 21 days. There was no statistically significant difference in HC duration between the two groups, with the median of 24 days (16, 32; 95% CI) in the intervention group (standard therapy + IVIG), and 24 days (2, 46; 95% CI) in control group, respectively (p=0.39). The median HC duration in MAC and RIC was 35 days (18, 52; 95% CI) versus 17 days (14, 20; 95% CI), respectively (p<0.01). The presence of GvHD I-IV at the time of HC symptoms manifestation was also characterized by positive correlation with HC duration. It was 36 days (22, 50; 95% CI) in patients with GvHD and 18 days (15, 21; 95% CI) in patients without GvHD (p=0.013).

Conclusions

Our data didn’t show any clinical efficiency of 1.2 g/kg IVIG (Immunovenin® 5%, 50mg/mL by Microgen) effectiveness in post allo-HSCT HC patients. Conditioning regimen intensity and GvHD I-IV are the risk factors for HC longer duration. The further prospective study is needed to make final conclusions on method’s effectiveness.

Keywords

Allogeneic hematopoietic stem cell transplantation, hemorrhagic cystitis, intravenous immunoglobulin, IVIG, risk factors, graft-versus-host disease (GvHD).
Introduction

Hemorrhagic cystitis (HC) is a frequent complication in allogeneic hematopoietic stem cell transplantation (allo-HSCT) with incidence of 9% to 31% for different cohorts [1-7]. Early clinical form of HC usually develops within ten days post allo-HSCT. In this cases HC is considered a direct consequence of cytotoxic conditioning therapy and graft-versus-host disease (GvHD) prophylaxis [8]. Along with cytotoxic drugs, some viral agents, e.g., BK- and JC- polyomaviruses, adenovirus and cytomegalovirus may be also involved in HC pathogenesis. Among them, human BK-polyomavirus (BKPyV) is the most frequently activated virus in urological setting, and, therefore, its elimination is a primary aim in HC treatment [8-12].

Some preclinical evidence for intravenous immunoglobulin (IVIG) effectiveness was reported earlier. Parmjeet S Randhawa et al. have demonstrated an ability of commercially available IVIG to neutralize BKPyV in human and mice cell cultures [13]. E.g., a 5-gram IVIG volume (one standard bottle) was able to inactivate 1.9*10^6 BKPyV/mL of plasma in 5,000 ml of blood, thus roughly corresponding to mean circulating blood volume in adults. It was, therefore, supposed that these preparations contain sufficient amounts of BKPyV-specific antibodies to neutralize clinically significant viral loads.

There is also some clinical evidence of IVIG effectiveness in BK virus nephropathy following renal transplantation. The latter condition has much common in origin with HC post allo-HSCT since it also occurs in immunocompromised host with preexisting urinary system lesions. The current treatment approaches for BKPyV nephropathy are immunosuppression reduction and IVIG administration at a total dose of 2 g/kg over 2-5 consecutive days [14, 15].

No standard strategy is, however, developed for HC treatment after allo-HSCT, as all the published data on IVIG treatment in these settings are limited to several case reports [16]. Despite the lack of available data, IVIG may be regarded as a feasible option based on its favorable safety profile and potential clinical efficiency [6].

It is even more notable, since some other established treatment options, e.g. intravenous Cidofovir infusions (CII evidence level) are, besides being potentially nephrotoxic, not currently available in Russian Federation. Meanwhile, the IVIG efficiency in HC has not been previously evaluated, although it is routinely used in our practice.

The current study is, therefore, aimed at evaluating the efficiency of IVIG infusions in HC patients after allo-HSCT, taking into account such additional clinical variables as conditioning regimen intensity and GvHD prophylaxis.

Materials and methods

A total of 1037 allo-HSCT recipients transplanted in R. M. Gorbacheva Memorial Institute for Pediatric Oncology, Hematology and Transplantation in 2013-2018 were included in the retrospective open single-center cohort study.

Hemorrhagic cystitis (HC) was registered in 118 cases (11.4%). According to inclusion criteria, only 90 patients were enrolled to the final analysis. This cohort was divided into two groups based on HC therapy used: the intervention group (n=42) included the patients with standard HC treatment with addition of IVIG; the control group (n=48) received standard HC therapy only. Patients developing allegedly cytotoxic HC before Day+7 post allo-HSCT and second allo-HSCT recipients were excluded from the analysis. Patients in the intervention group were also subdivided based on IVIG therapy timing, dose and duration. Only those patients were included who received IVIG for at least 3 days at the doses of >400 mg per kg, being administered not later than three days since HC onset.

HC diagnosis was based on the presence of hematuria and dysuria. The laboratory criteria included at least one episode of high-grade hematuria (>50 red blood cells per high-power field). The presence of GvHD I-IV was considered as an additional risk factor in statistical evaluation. The standard HC treatment, which all patients received, consisted of intensive IV fluids with forced diuresis, NSAIDs and antispasmodics. Elastic urinary catheters were used in cases of high-risk bladder tamponade, in order to provide bladder washing and evacuation of blood clots.

In the intervention group, we used a commercially available IVIG (Immunovenin® 5%, 50 mg/mL), manufactured by Microgen, Russia. The IVIG treatment began within the first three days since the HC onset, in most patients it was started within 24 hours. Estimation of treatment effectiveness was based on HC symptoms duration. These results were compared to the ones in the control group, which did not receive IVIG. Additional risk factors included conditioning regimen intensity, GvHD prophylaxis, and presence of GvHD.

Statistical evaluation

The data was analyzed with SPSS Statistics v.23 software. The groups were characterized via qualitative characteristics, which were grouped for comparison via chi-square test in conjugated tables. One sample Kolmogorov-Smirnov test used for testing if a variable follows a given distribution in a population. Mann-Whitney U test was used to compare outcomes between two independent groups. To compare HC duration depending on different factors (IVIG therapy, conditioning regimen intensity, and presence of GvHD) Kaplan-Meier curves were used. HC duration was a median (95% CI) according Kaplan-Meier test. The correlation strength was evaluated via log rank test. All values with significant correlation were combined as Cox regression model for multivariate analysis. The p values of ≤0.05 were considered statistically significant.

Results

The HC development rate in the total allo-HSCT recipient group (intervention and control) was 11.4% (n=118). Only 90 patients matched all the above clinical criteria and were included in the analysis, 42 of them (46.7%) fell into the intervention group (with IVIG), and 48 (53.3%), into control group. The median HC duration in common group was 21 days.
Both groups were balanced by gender, diagnosis (malignant and non-malignant conditions), donor type, hematopoietic stem cells (HSC) source, number of patients with clinical signs of GvHD at first signs of HC. The groups were different by two parameters: median age (17 in the intervention group, and 23 in control group, \( p=0.02 \)), and underlying malignant conditions spectrum (more ALL patients among IVIG recipients, and more AML patients in control group).

The majority of patients received allo-HSCT from unrelated donor (70.8% in the intervention group, and 71% in control group, respectively). There was no significant difference in HSC source between the groups. Bone marrow (BM) and peripheral blood stem cells (PBSC) were used 43.7% and 56.3% in the intervention group, and 45.2% and 54.8% allo-HSCT cases in control group, respectively. The patients’ characteristics are presented in Table 1.

A total IVIG dose ranged from 1.2 g/kg to 4 g/kg was used (usually 400 mg/kg/day for 3 consecutive days, except one patient with 10-days IVIG treatment) with a median single dose of 1.2 g/kg and a median total dose of 35 g per patient. There was no statistically significant difference in HC duration between groups with the median of 24 days (16, 32; 95% CI) in the intervention group and 24 days (2, 46; 95% CI) in control group, respectively (\( p=0.39 \); Fig. 1).

The main factors affecting HC duration were conditioning regimen intensity, presence of GvHD at the moment of the first HC signs. The median HC duration in MAC and RIC recipients were 35 days (18, 52; 95% CI) and 17 days (14, 20; 95% CI), respectively (\( p<0.01 \); Fig. 1).

The presence of GvHD I-IV at the time of HC symptoms manifestation was also characterized by positive correlation with HC duration. It was 36 days (22, 50; 95% CI) in patients with, and 18 days (15, 21; 95% CI) in patients without active GvHD (\( p=0.013 \)).

### Table 1. Characteristics of patients with hemorrhagic cystitis in IVIG-treated and control groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention (n=42)</th>
<th>Control (n=48)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>17 (3-55)</td>
<td>23 (7-70)</td>
<td>0.02</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (69%)</td>
<td>28 (58.3%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Female</td>
<td>13 (31%)</td>
<td>20 (41.7%)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td>&gt;0.01</td>
</tr>
<tr>
<td>AML</td>
<td>10 (23.8%)</td>
<td>26 (54.2%)</td>
<td></td>
</tr>
<tr>
<td>ALL</td>
<td>25 (59.5%)</td>
<td>14 (29.2%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7 (16.7%)</td>
<td>8 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>Non-malignant diseases</td>
<td>40</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Donor type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-matched related</td>
<td>2 (10.5%)</td>
<td>6 (15.5%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Unrelated</td>
<td>25 (71%)</td>
<td>34 (70.8%)</td>
<td></td>
</tr>
<tr>
<td>Haploidentical</td>
<td>15 (18.4%)</td>
<td>8 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>HSC source</td>
<td></td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>BM</td>
<td>19 (45.2%)</td>
<td>21 (43.7%)</td>
<td></td>
</tr>
<tr>
<td>PBSC</td>
<td>23 (54.8%)</td>
<td>27 (56.3%)</td>
<td></td>
</tr>
<tr>
<td>Conditioning regimen</td>
<td></td>
<td></td>
<td>0.44</td>
</tr>
<tr>
<td>MAC</td>
<td>27 (64.2%)</td>
<td>27 (56.3%)</td>
<td></td>
</tr>
<tr>
<td>RIC</td>
<td>15 (35.8%)</td>
<td>21 (43.7%)</td>
<td></td>
</tr>
<tr>
<td>GvHD I-IV</td>
<td>Yes</td>
<td>27 (64.2%)</td>
<td>0.56</td>
</tr>
<tr>
<td>No</td>
<td>15 (35.8%)</td>
<td>20 (41.7%)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Cox proportional hazard regression model data for the three studied clinical parameters in HSCT patients with hemorrhagic cystitis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Significance</th>
<th>Exp (B)</th>
<th>CI 95.0% for Exp(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>lower</td>
</tr>
<tr>
<td>IVIG / ST</td>
<td>0.615</td>
<td>1.126</td>
<td>0.710</td>
</tr>
<tr>
<td>MAC / RIC</td>
<td>0.003</td>
<td>1.750</td>
<td>1.070</td>
</tr>
<tr>
<td>GvHD (+) / (-)</td>
<td>0.026</td>
<td>2.176</td>
<td>1.311</td>
</tr>
</tbody>
</table>
Clinical Studies

Figure 1. Univariate analysis (Kaplan-Meier method) of HC cumulative incidence in the intervention group and control group, then based on conditioning regimen intensity (MAC vs RIC), and presence of GvHD I-IV at the time of HC manifestation.

The multivariate analysis was performed by Cox proportional-hazard regression model including the following factors: IVIG vs no IVIG in therapy regimen, conditioning regimen intensity (MAC vs RIC), and presence of HC at the time of HC symptoms onset. It has shown MAC and GvHD presence to be independent risk factors associated with longer HC duration (Table 2).

Discussion

While there was no statistically significant difference between cohorts in our study, it had some significant limitations, which could compromise the results: the retrospective design of the study, single-center experience and unknown HC etiology; varied IVIG doses – the median single dose was 1.2 g/kg, which is significantly lower than dose recommended for patients with BKPyV-associated nephropathy (2 g/kg) [14, 15]. Therefore, the IVIG therapy at the dose recommended for BKPyV-associated nephropathy may still be effective.

According to World Health Organization Model Formulary 2008, Chapter – IVIG: "Formulations from different manufacturers vary and should not be regarded as equivalent" [17]. IVIG can have significant differences not only between manufacturers and commercial brands, but also between series of the same drug, which is well discussed by Nathaniel Washburn et al. It is a challenge to assess the influence of these data on clinical effectiveness, especially when IVIG mechanism of action in HC is partly unclear. Also there is lack of data in drug's instructions for use, given by manufacturers about IVIG class and mechanism of action [18]. The prospective study design involving higher IVIG doses (at least 2 g/kg) and from different manufactures could be more exemplary.

According to ECIL (European Conference on Infections in Leukaemia) 2018 guidelines on post allo-HSCT BK-associated HC, IVIG therapy is not recommended as a routine treatment option and graded experimental among such methods as intravesical Cidofovir or Sodium Hyaluronate infusions, iv estrogens, mesenchymal cells etc. This is explained by current lack of evidence with most evident-based method (AIII level) being best supportive care consisting of hydration, platelets transfusion and pain control [6]. Our data is also not yet sufficient to recommend IVIG as a standard treatment option.

Many researches have demonstrated the association between conditioning regimen intensity and HC incidence, some of them presumed cyclophosphamide toxicity, but this link has not always been confirmed [19-25]. The reasons for GvHD association with HC development are not yet completely clear. The direct immune damage hypothesis has not been proved [26, 27]. However, as GvHD treatment causes additional severe immunosuppression, viral reactivation and active replication may appear which may be a direct cause of HC [28]. We demonstrated the association between certain risk factors (condition regimen intensity and concurrent GVHD) and not only HC incidence, but also its duration, which may be due to stronger immunosuppression in these conditions.

Conclusions

Our data didn’t prove superior therapeutic effect of 1.2 g/kg IVIG (Immunovenin® 5% (50mg/ml) by Microgen) in post allo-HSCT HC patients. Conditioning regimen intensity and GVHD I-IV are the risk factors for HC longer duration. A further prospective study is needed to make final conclusions on method's effectiveness.

Conflict of interest

None declared.

References

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Оценка эффективности внутривенного иммуноглобулина G в терапии геморрагического цистита при аллогенной трансплантации гемопоэтических стволовых клеток

Александр А. Щербаков, Алена Н. Зайцева, Максим А. Кучер, Ирина С. Ярушкина, Ольга Н. Зацепина, Екатерина С. Кульгина, Олеся В. Панина, Руслана В. Клементьева, Олег В. Голощапов, Иван С. Моисеев, Людмила С. Зубаровская, Борис В. Афанасьев

НИИ детской онкологии, гематологии и трансплантологии им. Р. М. Горбачевой, Первый Санкт-Петербургский государственный медицинский университет им. акад. И. П. Павлова, Санкт-Петербург, Россия

Резюме
Геморрагический цистит (ГЦ) – это частое осложнение при аллогенной трансплантации гемопоэтических стволовых клеток (алло-ТГСК). Персистирование BK полиомавируса (BKPyV) является одной из основных предполагаемых причин, приводящих к развитию позднего ГЦ после алло-ТГСК. Имеются доклинические данные об эффективной нейтрализации BKPyV внутривенным иммуноглобулином G (ВВИГ) в клеточных культурах, а также при BK вирусной нефропатии при трансплантации почки.

Пациенты и методы
Ретроспективно было изучено 1037 пациентов получивших алло-ТГСК в НИИ детской онкологии, гематологии и трансплантологии им. Р.М. Горбачевой с 2013 по 2018 год. ГЦ был зарегистрирован в 118 (11,4%) случаях, из них, согласно критериям включения, 90 пациентов включены в анализ: группа сравнения с ВВИГ (n=42) и контрольная группа (n=48) со стандартной терапией ГЦ.

Результаты
Продолжительность ГЦ в общей группе составила 21 день. Не было статистически значимой разницы в продолжительности ГЦ между группой сравнения и контрольной группой – медиана 24 дня (16, 32; 95% СИ) и 24 дня (2, 46; 95% СИ), соответственно (p=0,39).

Одновременное наличие симптомов ГЦ и РТПХ I-IV степени, также характеризовалось положительной корреляцией с длительностью ГЦ – 36 дней (22, 50; 95% ДИ) у пациентов с РТПХ и 18 дней (15, 21; 95% ДИ) у пациентов без РТПХ, p=0,013.

Выводы
Настоящее исследование не подтвердило клиническую эффективность ВВИГ (Иммуновенин 5% (50мг/мл) Микроген) в дозе 1,2 гр/кг у пациентов с ГЦ после алло-ТГСК. Факторами риска более длительного течения ГЦ были интенсивность режима кондиционирования и наличие РТПХ I-IV степени. Требуется проведение проспективного исследования для определения эффективности ВВИГ в качестве терапии позднего ГЦ после алло-ТГСК.

Ключевые слова
Аллогенная трансплантация гемопоэтических стволовых клеток, геморрагический цистит, внутривенный иммуноглобулин, ВВИГ, факторы риска, реакция «трансплантат против хозяина» (РТПХ).