Importance: It is essential to have insights into the risk of ocular involvement after hematopoietic stem cell transplantation (HSCT) in the pediatric population because young and severely ill children are unaware of their ocular problems.

Objective: To study the development of ocular complications in children within 1 year after HSCT.

Design and Setting: This prospective study includes all consecutive patients who had undergone an HSCT at the Wilhelmina Children’s Hospital, University Medical Center Utrecht, Utrecht, the Netherlands, in 2009 and 2010.

Participants: Forty-nine consecutive patients underwent systematic ophthalmologic evaluations before HSCT, before leaving the HSCT unit after HSCT, and 3, 6, and 12 months after HSCT. Additional examinations were performed during systemic viral reactivations.

Main Outcome Measure: Development of ocular complications, including uveitis, hemorrhagic complications, optic disc edema, and dry eye syndrome.

Results: Thirteen patients (27%) developed an ocular complication after HSCT. These complications included DES (n=7 [14%]), (sub)retinal hemorrhage (n=6 [12%]), optic disc edema (n=3 [6%]), chorioretinal lesions (n=2 [4%]), vitritis (n=1 [2%]), and increased intraocular pressure (n=1 [2%]). Median time to the development of dry eye syndrome was 5 months after HSCT, whereas all other ocular complications were detected within the first 3 months after HSCT. In most cases, the symptoms were mild and self-limiting. Children with malignant disease had a higher risk of the development of ocular complications compared with children with nonmalignant disease.

Conclusions and Relevance: Ocular complications in pediatric HSCT patients are common, although mostly mild. The risk of viral uveitis development during systemic viral reactivations is low; however, the potential risk of vision-threatening complications in this population cannot be ruled out.


METHODS

This prospective study includes all consecutive patients who had undergone HSCT at the Wilhelmina Children’s Hospital, University Medical Center Utrecht, Utrecht, the Netherlands, in 2009 and 2010. This population includes children 18 years or younger, except one 22-year-old patient, who had undergone HSCT in the...
children’s hospital. Transplantation details, conditioning regimens, supportive care, graft-vs-host disease (GVHD) prophylaxis, and infection monitoring within the Pediatric Blood and Marrow Transplantation Program of the Wilhelmina Children’s Hospital have been extensively described previously. The study was performed with the approval of the institutional review board of Utrecht Medical Center.

Viral pre-HSCT prophylaxis was given only in cases of positive serologic test results for herpes simplex virus (HSV) (with intravenous acyclovir during neutropenia and oral acyclovir with valacyclovir hydrochloride after neutropenia until the CD4⁺ cell count was >200/μL). Total IgG levels were checked every 2 weeks; intravenous immunoglobulin was given only to those patients with an IgG level less than 400 mg/dL (to convert to grams per liter, multiply by 0.01). For viral monitoring, plasma samples were tested weekly for cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6), and adenovirus DNA positivity by qualitative real-time polymerase chain reaction. Viral reactivation was diagnosed when counts were greater than 1000 copies/mL. Adenovirus, CMV, EBV, and HHV-6 were preemptively treated according to local guidelines. The skin was checked for HSV and varicella-zoster virus (VZV) reactivation during physical examinations.

Graft-vs-host disease prophylaxis consisted of cyclosporine (aiming for a trough level of 100-250 μg/L, based on national protocol guidelines), supplemented with methylprednisolone sodium succinate in patients receiving a cord blood transplantation, or a short course of methylprednisolone in patients receiving an unrelated bone marrow or peripheral blood stem cell transplantation. In patients receiving an unrelated donor graft, antithymocyte globulin serum therapy was added to the conditioning regimen. The skin was checked for HSV and varicella-zoster virus (VZV) reactivation during physical examinations.

Ophthalmologic examinations were performed by pediatric ophthalmologists, and all children were additionally examined by an orthoptist. All included children had an ophthalmologic evaluation before HSCT. After HSCT, the patients were regularly examined before leaving the HSCT unit (median time of 3 weeks after HSCT) and at 3, 6, and 12 months after the HSCT. Additional ophthalmologic examinations were performed in cases of a viral reactivation of adenovirus, CMV, EBV, HHV-6, HSV, and VZV and/or if ocular symptoms were present. Standard ophthalmologic examination included, if possible, visual acuity measurement, slitlamp examination (including fluorescein staining of the cornea), and funduscopy with a dilated pupil at the HSCT unit. In patients with ocular symptoms, visual acuity measurement and a hand slitlamp examination were also performed.

Dry eye syndrome (DES) was defined as the presence of corneal epithelial staining in combination with a reduced tear film by slitlamp examination. The Schirmer test was not performed routinely because of the limited cooperation of young children, general illness, or both.

For statistical data analysis, SPSS statistical software, version 15.0.1 (SPSS, Inc), was used. The Fisher exact test was used for analysis of categorical variables (to compare patients with malignant and nonmalignant disease). The Mann-Whitney test was used for analysis of age differences between patients with and without DES and hemorrhagic complications. A Kaplan-Meier analysis was used for a curve of cumulative incidence of ocular complications after HSCT. The Cox proportional hazards regression model was used to analyze associations between baseline variables and the development of DES and hemorrhagic complications. To analyze predictors for the development of these complications, we considered the recipient-associated variables of age at HSCT, sex, and malignant disease and the transplantation-associated variables of source of stem cells, HLA disparity, and the basis of the conditioning regimen (chemotherapy or total body irradiation).

RESULTS

A total of 49 patients were included in this study. Forty-eight patients underwent allogenic HSCT and 1 patient autologous HSCT. In 2 patients, an allogenic HSCT was preceded by an autologous HSCT. Demographics, indications for HSCT, and main patient characteristics are given in Table 1.
OPHTHALMOLOGIC FINDINGS BEFORE HSCT

Ophthalmologic evaluation before HSCT revealed abnormal findings in 4 of 49 patients (8%) who had previously not undergone transplantation. These findings included mild DES (n = 2), retinal hemorrhages (n = 1, also DES was present simultaneously in this patient), optic disc edema (n = 1), and chorioretinal scars (n = 1; Table 2). Bilateral mild swelling of the optic disc was detected before HSCT in 1 patient with acute lymphoblastic leukemia (ALL) without any signs of intraocular inflammation. The finding could not be clarified by a relapse of the underlying disease or raised intracranial pressure or toxic effect. Peripheral, chorioretinal, punched-out lesions were detected before HSCT in a patient with X-linked chronic granulomatous disease. The lesions appeared inactive and were clinically consistent with chorioretinal lesions that have been previously described for patients with this disorder.20-23

Table 2. Abnormal Eye Conditions Detected in Pediatric Patients Before and Within 1 Year After HSCT

<table>
<thead>
<tr>
<th>Abnormal Eye Condition</th>
<th>No. (%) of Children (N = 49)</th>
<th>Time After HSCT, Median (Range)</th>
<th>HSCT Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ocular abnormalities</td>
<td>4 (8)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>DES</td>
<td>2 (4)</td>
<td>7 (14)</td>
<td>5 mo (3 wk-12 mo)</td>
</tr>
<tr>
<td>(Sub)retinal hemorrhage</td>
<td>1 (2)</td>
<td>6 (12)</td>
<td>3 wk (2-5 wk)</td>
</tr>
<tr>
<td>Optic disc edema</td>
<td>1 (2)</td>
<td>3 (6)</td>
<td>3 wk (3-5 wk)</td>
</tr>
<tr>
<td>Chorioretinal lesions</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>3 and 5 wk</td>
</tr>
<tr>
<td>Vitritis</td>
<td>NA</td>
<td>1 (2)</td>
<td>3 mo (NA)</td>
</tr>
<tr>
<td>Increased intraocular pressure</td>
<td>NA</td>
<td>1 (2)</td>
<td>3 mo (NA)</td>
</tr>
</tbody>
</table>

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myelogenous anemia; CGD, chronic granulomatous disease; DES, dry eye syndrome; HSCT, hematopoietic stem cell transplantation; MDS, myelodysplastic syndrome; NA, not applicable; NHL, non-Hodgkin lymphoma.

a New-onset ocular findings after HSCT. The percentages are computed regardless of loss to follow-up.

OPHTHALMOLOGIC FINDINGS AFTER HSCT

New abnormal eye conditions were detected in 13 patients (27%) within 1 year after HSCT. Table 2 gives an overview of detected abnormalities, the moment of their detection, and the underlying diseases of the affected patients. Seven patients (14%) developed DES, and the remaining patients had retinal hemorrhages (n = 6 [12%]), optic disc edema (n = 3 [6%]), chorioretinal lesions (n = 2 [4%]), vitritis (n = 1 [2%]), and increased intraocular pressure (n = 1 [2%]) (Table 2). Figure 1 shows the cumulative incidence curve of ocular complications.

Abnormal Findings in the Early Posttransplantation Period (Within the First 3 Months After HSCT)

Systemic viral reactivations occurred in 20 patients (9 patients with CMV, 6 patients with VZV, 4 patients with HHV-6, 3 patients with adenovirus, and 2 patients with EBV; in 4 patients >1 different viral reactivation occurred). All patients underwent ophthalmologic examination at the time of viral reactivations, but no new ocular abnormalities were observed.

However, new asymptomatic chorioretinal scars were detected within 3 and 5 weeks after HSCT in 2 patients with ALL after having systemic CMV (treated with foscarnet sodium) and VZV (treated with valacyclovir) reactivations in an early posttransplantation period (Table 2). Round multiple central and peripheral punched-out lesions were located bilaterally in the young patient with previous VZV reactivation (Figure 2). The patient with previous CMV reactivation developed multiple, round, punched-out lesions located only peripherally. No active intraocular inflammation was observed; therefore, no additional diagnostic procedures were performed.

Retinal hemorrhages were detected in 6 patients (12%) (Table 2). In all of these patients, the hemorrhages were located intraretinally, in one of them in combination with a subretinal hemorrhage. Hemorrhagic complications typically developed in the early posttransplantation period (Table 2). The hemorrhages did not threaten the vision and were in all cases associated with a deep thrombocytopenia (lowest thrombocyte count in 2 weeks before the hemorrhage, 4-24 × 10^9/μL [to convert to 10^12/L, multiply by 1]). The hemorrhages resolved after improvement of thrombocytopenia. Children with hemorrhagic complications...
were significantly older than children without hemorrhages (median age, 17.6 vs 5.7 years, respectively; \( P = .005 \)). Development of hemorrhagic complications was independently associated with older age at HSCT (Table 3).

Optic disc edema was seen in 3 patients (6%) (Table 2). One patient with ALL and a mild idiopathic bilateral swelling of the optic disc before HSCT developed a significant increase of the edema after HSCT (Figure 3) during systemic administration of cyclosporine. An extensive diagnostic workup excluded increased intracranial pressure, infection, or central nervous system relapse of leukemia. The remaining 2 cases of optic disc edema in the post-HSCT period were detected within the first 5 weeks after HSCT. In both patients, optic disc edema was transient (one had bilateral edema and the other had unilateral edema), and the cause(s) remained unidentified.

In 1 patient without concurrent proved infection, a mild bilateral vitritis with hyperemic optic discs was seen at 3 months after HSCT. At that time, no blasts were in the patient’s peripheral blood; however, 1 month later, a relapse of acute myeloblastic leukemia was diagnosed, and the patient died before the next planned ocular examination.

Bilaterally increased intraocular pressure of 25 mm Hg was detected in 1 patient at 3 months after HSCT in combination with bilaterally new-onset small excavations of optic discs during administration of oral corticosteroids. The patient died before the next planned ocular examination.

Abnormal Findings Later in the Posttransplantation Period (3-12 Months After HSCT)

New-onset DES was observed in 7 of 49 patients (14%) (Table 2). Median time to detection of DES was 5 months (range, 3 weeks to 12 months). Although in our study DES was typically a later finding, 2 patients who had not previously undergone transplantation had signs of DES within 3 months after HSCT.

In 4 of 7 patients with DES (57%), the findings were accompanied by characteristic systemic manifestations of acute (\( n = 2 \)) and/or chronic (\( n = 3 \)) GVHD in at least 1 other organ. In patients without DES, systemic GVHD was diagnosed in 31%; however, this difference was not statistically significant. Patients with DES were significantly older than other patients (median age, 13.7 vs 5.5 years; \( P = .003 \)). One patient with systemic GVHD developed severe DES, which required intensive therapy, including lubricants, corticosteroid eye drops, cyclosporine ointment, autologous serum eye drops, and bandage contact lenses. This patient subsequently developed herpetic keratitis. All other cases of DES were relatively mild.
and the symptoms could be well controlled with (temporary) administration of lubricants (n = 5) or even without therapy (n = 1). Development of new-onset DES after HSCT was independently associated with older age and malignant tumor as indications for HSCT (Table 3).

In general, patients with any ocular complication after HSCT were significantly older than patients without complications (median age, 13.3 vs 3.4 years; P < .001). Of 13 patients with ocular abnormalities in the posttransplantation period, 12 (92%) had a malignant disease. Of the patients with malignant disease, 12 of 28 (42%) developed ocular abnormalities compared with 1 of 21 patients (4%) with nonmalignant disease (relative risk = 10.5; P = .003).

Four patients had multiple abnormal ocular findings after HSCT. All of them had signs of DES in combination with other complications. Only 5 of 13 patients (38%) with ocular abnormalities had subjective symptoms: 4 with DES and 1 with optic disc edema. Although patients with abnormal ophthalmologic findings seemed to have higher mortality within the first year after HSCT than patients without ocular complications (38% vs 23%), this difference was not statistically significant (P = .48).

**COMMENT**

During this prospective study, no signs of active viral, fungal, or bacterial infections of the eye were detected, despite the fact that 20 (41%) of the 49 patients developed a systemic viral reactivation. However, new-onset, inactive chorioretinal scars were observed in 2 patients after recovery from a viral reactivation, but their potential infectious cause remained unclear. Ocular abnormalities were detected in 13 (27%) of the 49 pediatric HSCT patients in the studied cohort within 1 year after an HSCT. Most of the detected abnormalities were relatively mild and not vision threatening, with DES and retinal hemorrhages as the most frequent findings. Ocular abnormalities were observed significantly more frequently in patients with malignant disease.

Opportunistic infections of the eye fortunately seem to be rare in children,3,4,7,8,12-14 a finding consistent with our observations. Low incidence of these vision-devastating complications is an assumable result of significant progress in the prevention of the posttransplantation infections in HSCT patients. In our study, new chorioretinal lesions were detected in the early posttransplantation period in 2 boys with ALL (the areas of the lesions were definitively previously examined at the time of viral reactivation). These lesions were similar to the lesions of a patient with ALL described previously by Ng et al.8 Both of our patients had a history of a systemic viral reactivation in an early posttransplantation period and were treated with antiviral agents. The character of the chorioretinal lesions was not typical for CMV retinitis or VZV1,11 although the possibility of transient local retinitis under administration of antiviral agents cannot be excluded. The hypothesis of choroidal vascular occlusions as a cause of these lesions was suggested, however, the history of our patients provides no support for this assumption.

The underlying cause of mild vitritis detected in 1 patient at 3 months after HSCT can only be speculated. Because of the relapse of AML 1 month later, vitritis and hyperemic optic discs could be signs of an ocular masquerade syndrome.

Cumulative ocular complication rates in the pediatric HSCT population reported in retrospective studies varied between 33% and 51%.6,7 These complication rates also included such long-term complications as cataracts, whereas the focus of our prospective study was set on type and timing of ophthalmologic abnormalities within the first year after HSCT. One retrospective study3 reports a 1-year posttransplantation ocular complication rate of 16%, but it encompasses both bone marrow and organ transplantation recipients. A retrospective character of this study could clarify differences in reported complication rates with our study. The complication rate of our study is calculated regardless of loss to follow-up, so the reported incidence could be underestimated.

Our most frequent ocular finding after HSCT was DES with corneal staining, which was detected in 7 (14%) of 49 patients. Earlier retrospective and cross-sectional pediatric reports8,6,4 have described the occurrence of DES with corneal staining as ranging from 4% to 62%. An outlier of 62% could be caused by a significantly older population (median age, 15.6 years) and a longer follow-up (median, 7 years) in that particular study.6 We found a significant association of DES with older age in a pediatric/young adult population after HSCT, which was noted previously.6 This association is supported by the previously described continual decline in tear function with age24 and the association of older age with development of systemic GVHD.25-27 which seems to be the main underlying reason of DES after an HSCT.7,8,28 Younger patients probably have better thymic function and higher regenerating ability of cells damaged by GVHD. We also found an association of DES development with malignant disease as an indication of HSCT. The increased risk of ocular complications in children with malignant disease after HSCT was described previously.7 An explanation may be the fact that immunosuppressive agents are tapered earlier in an individual with malignant disease compared with patients with nonmalignant indications. Earlier taper may be associated with some more alloreactivity in the eye and other organs. Other factors that are traditionally associated with the development of DES after HSCT are total body irradiation and chemotherapy.6,28 We did not find these associations in our population.

It has been suggested that many children may already have DES before HSCT.6 We cannot confirm this statement because in our prospective study, only 2 (4%) of our 49 patients who had not previously undergone transplantation were diagnosed as having mild symptom-free DES before HSCT.

Hemorrhagic complications in the early posttransplantation period were the second most frequently detected abnormality in our study. Our findings agree with previous studies1,4 in children and adults that also report hemorrhagic (pre)retinal complications associated with low platelet count within the first 6 months after HSCT. However, the reported frequency of hemorrhagic complications (3%, 5%, and 4%) seems to be underestimated in these studies because of their retrospective nature and the asymptomatic and transient character of the hemorrhages.
The frequency of optic disc edema found in our study (n = 3; 6%) is similar to previous reports in children and adults (3%-5%).1,4,7,11 The exact cause of the optic disc edema is unknown, but the possibility of cyclosporine toxicity was previously suggested.1,4,11 This cause was also presumed in 2 of our patients with transient bilateral optic disc edema with an improvement once the dose of cyclosporine was adjusted. However, unilateral disc edema related to the cyclosporine toxicity is unlikely.

Cataracts are an important delayed ocular complication of HSCT repeatedly reported in children at varying prevalences of 6% to 58%, depending on duration of follow-up and conditioning regimens.3-5,7,8 Cataracts are a rare finding within the first year after HSCT.3-5,7,8 In our study, which was limited to 1-year follow-up, we did not detect any clinically significant lens opacities. It may be of interest to examine the patients included in this cohort in 5- and 10-year periods again.

Most of the complications detected in our study were mild; however, the potential risk of development of vision-threatening complications in this population remains. The main goal of posttransplantation screening within the first year after HSCT should be a limitation of eventual damage and long-term visual sequelae. Because no preventable causes of decreased vision were detected during screening in our series, the question remains whether ophthalmic screening of all children after HSCT is useful. Nevertheless, we recommend a pre-HSCT examination for detecting ocular abnormalities that require prophylactic treatment during the immunosuppression period, for example, chorioretinal scars caused by infections, which can reactivate after HSCT, despite the absence of such cases in this particular study. Pre-HSCT screening is also essential for better appreciation of eventual chorioretinal changes after HSCT.

In conclusion, ocular adverse effects in pediatric HSCT patients are common, but most are mild with no long-term visual sequelae; however, a potential risk of development of vision-threatening complications cannot be ruled out completely in this vulnerable group of patients. The results of our study do not allow concluding that a more aggressive screening program is useful. Both ophthalmologists and pediatrics should be aware of higher risk of the development of ocular complications with malignant disease.

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REFERENCES