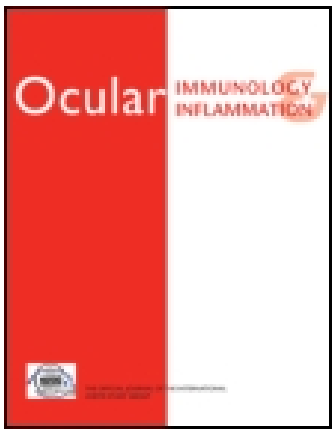

Ocular Immunology and Inflammation
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/ioii20

Absence of Intraocular Infections after Hematopoietic Stem Cell Transplantation at a Single Center: The Experience with Current Preventive Regimens

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Published online: 16 May 2015.

Ocular Immunology & Inflammation, 2014; 22(2): 116–120

ISSN: 0927-3948 print / 1744-5078 online
DOI: 10.3109/09273948.2013.827216

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ORIGINAL ARTICLE

Absence of Intraocular Infections after Hematopoietic Stem Cell Transplantation at a Single Center: The Experience with Current Preventive Regimens

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ABSTRACT

Purpose: To investigate the prevalence of intraocular infections after allogeneic stem cell transplantation (allo-SCT).

Methods: The study design was a single institutional retrospective noncomparative cohort of 135 consecutive patients in 2006 and 2007 who underwent allo-SCT for hematological malignancy. The primary outcome was the development of intraocular infections after allo-SCT and secondary outcome consisted of development of other ocular disorders during follow-up.

Results: The most frequent ocular sequel to allo-SCT included ocular graft-versus-host disease (GvHD), which developed in 37/135 patients (27%). Intraocular infection occurred in 1 of 135 patients (0.7%). This patient developed infectious chorioretinitis together with osteomyelitis, endocarditis, and brain abscess with fungus *Scedosporium* and was successfully treated with a combination of voriconazole, amphotericine B, and surgical interventions. Viral and/or bacterial intraocular infections were not observed at all.

Conclusions: Intraocular infections after allo-SCT are currently uncommon due to systematic use of preemptive treatment regimens, frequent controls, and early treatment of systemic infections.

Keywords: Allogeneic stem cell transplantation, antibiotics, antiviral treatment, ocular infection, prophylactic treatment

INTRODUCTION

Severe sight-threatening ocular infections can occur after allogeneic stem cell transplantation (allo-SCT).[1] The use of conditioning regimens and immunosuppressive drugs improves the overall success rate and increases the chance of survival after allo-SCT, but also increases the risk of developing bacterial, viral, and fungal infections.[2,3] After allo-SCT, all patients receive preventive antibiotic treatment during the period of immune insufficiency[4] and are frequently assessed for systemic infections and/or reactivations. There is a lack of available data on the prevalence of ocular infections after allo-SCT in patients who received current prophylactic regimens for prevention of infections. The objective of the present study is to report on the up-to-date prevalence of intraocular infections after SCT in the adult population in terms of the efficacy of the tailored prophylactic regimen.

SUBJECTS AND METHODS

This study was approved by the institutional review board and is in compliance with the Declaration of Helsinki.

Received 23 February 2013; revised 27 May 2013; accepted 17 July 2013; published online 8 October 2013

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TABLE 1. Immunosuppressive treatment after allogeneic stem cell transplantation (allo-SCT).

Subtype of allo-SCT	Immunosuppressive treatment	Durations (days)
NMA MUD	1. Cyclosporine 4.5 mg/kg 2/day po 2. Mycophenolate 15 mg/kg 3/day po	1. D-3 to D + 180[a] 2. D0 to D + 84[b]
NMA matched sibling	1. Cyclosporine 6.25 mg/kg 2/day po 2. Mycophenolate 15 mg/kg 3/day po	1. D-3 to D + 180[a] 2. D0 to D + 84[b]
MA MUD and	1. Cyclosporine 1.5 mg/kg/24 h 2/day iv Cyclosporine 2/day po[c]	1. D-3 to D + 20 D + 21 to D + 180[a]
MA matched sibling	2. Mycophenolate 15 mg/kg 3/day iv Mycophenolate 15 mg/kg 3/day po[d]	2. D-0 to D + 20 D + 21 to D + 84[b]

D, day; NMA, nonmyeloablative; MA, myeloablative; MUD, HLA- matched unrelated donor; po, per os; iv, intravenous.
[a]After D + 180 10% weekly dose reduction, if until D + 120 no GvHD, reduced in 2 weeks.
[b]Dose reduction in 2 weeks after D + 84.
[c]Oral dose adapted according to referential blood values of 0.2–0.4 mg/L.
[d]Maximal dose mycophenolate 1 g 3/day po.

Patients

In this retrospective cohort study all adult patients who received allo-SCT between January 2006 and December 2007 at the University Medical Center Utrecht (UMCU), The Netherlands, were included. All patients received ophthalmic examination as part of an active screening protocol starting 3 months post-SCT or earlier in the case of ocular complaints or increased risk of developing an intraocular infection due to systemic infection. The examination consisted of registration of ocular and medical history, evaluation of current eye complaints, visual acuity test, slit-lamp examination with additional fluorescein staining, intraocular pressure measurement, followed by Schirmer test with local anesthetic and dilated fundus examination.

Medical Data

Data collection included demographic characteristics; cytomegalovirus (CMV) and Epstein-Barr virus (EBV) serologic status of donors and recipients; type of immunosuppressive therapy; type of post-SCT prophylaxis; onset, type, and treatment of systemic and intraocular infections; visual acuity (VA) during and if applicable after (intra)ocular infection; additional ocular complications and the presence of systemic and ocular graft-versus-host disease (GvHD). If multiple SCTs were performed, the follow-up time was considered the time between the last allo-SCT and the last medical assessment at the UMCU.

Post-Transplantation Procedure

The post-SCT immunosuppressive protocol is described in Table 1. All patients received co-trimoxazol 480 mg qd and valaciclovir 500 mg bid for 18 months. Ciproxin 500 mg bid po and fluconazole 150 mg qd po were administered during the post-SCT neutropenic state. Additional antiviral (valganciclovir) and antifungal (voriconazol) treatment was used in case of infection/reactivation with CMV and *Aspergillus*, respectively.

RESULTS

Subjects

A total of 140 patients were included in the study. Five patients were excluded from the study due to incomplete medical records. The basic characteristics of the study population are described in Table 2. The median follow-up time was 15 months, ranging from 1 to 74 months. The cause of limited follow-up included mostly death and in 1 case referral to another hospital for follow-up. All patients had ocular examination 3 months after allo-SCT, 61/135 (45%) patients received an ophthalmic examination repeated at 1-year follow-up and 74/135 (55%) at 2-year follow-up. Seventy patients (52%) were alive at the time of data analysis. The median time of all patients who have died was 6 months (range 1–50 months) in comparison to all living patients, whose median follow-up time was 51 months (range 2–74 months).

Systemic Infectious Sequelae

Fifty-nine patients (44%) developed systemic infection(s) or reactivations, of which 22 (16%) had simultaneously two or more infectious agents (see Table 2). The median time of development of systemic infection or reactivation since last-SCT was 2 months (range, 0.03–56.52 months). The most common was CMV

TABLE 2. Demographic characteristics of allogeneic stem cell transplantation (allo-SCT) patients.

Males, *n* (%)	82/135 (61)
Age, median (range)	56.0 (21–73)
Diagnosis, *n* (%)	
ALL	13/135 (10)
CLL	9/135 (7)
AML	35/135 (26)
CML	9/135 (7)
NHL	22/135 (16)
HL	7/135 (5)
MM	25/135 (19)
Other	15/135 (11)
Systemic opportunistic infection/ reactivation, *n* (%)	59/135 (44)
One agent	37/135 (27)
Two or more agents	22/135 (16)
Follow-up to systemic infection/ reactivation, median months (range)	2.49 (0.03–56.52)
Donor, *n* (%)	
MUD	77/135 (57)
Matched sibling	52/135 (39)
Other	6/135 (5)

ALL, acute lymphatic leukemia; CLL, chronic lymphatic leukemia, AML, acute myeloid leukemia; CML, chronic myeloid leukemia; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; MM, multiple myeloma; MUD, HLA-matched unrelated donor.

TABLE 3. Median interval between last allo-SCT and systemic reactivation and/or infection(s).

Opportunistic agent	Median in months (minimum–maximum)
CMV reactivation and/or infection, *n* = 36/135 (27%)	1.46 (0.03–56.52)
EBV reactivation and/or infection, *n* = 15/135 (11%)	1.77 (0.49–22.43)
Aspergillus pneumoniae, *n* = 12/135 (9%)	4.46 (0.26–31.44)

CMV, cytomegalovirus; EBV, Epstein-Barr virus.

reactivation, occurring in 27% of the patients, followed by EBV reactivation and/or infection and *Aspergillus pneumoniae*, detected in 11% and 9%, respectively. One patient (1%) with CMV reactivation was co-infected with human herpes virus type 6 (HHV6). The median reactivation times are described in Table 3. In 14 patients (10%) the specific origin of infection was either unknown or of a nonopportunistic origin. None of the patients has developed infection with *Toxoplasma*. A total of 105 patients developed systemic GvHD (78%), of which 45 (33%) had acute GvHD and 60 chronic GvHD (44%). Of the patients with systemic opportunistic reactivations or infections, 84% had concurrent systemic GvHD and 22% had a concurrent ocular GvHD.

Ocular Infectious Sequelae

Only 1 patient (0.7%) developed an intraocular infection. The infectious agent was a fungus (*Scedosporium apiospermum*) and this infection developed 6 months after allo-SCT (see selected case report later in the results section). None of the patients developed bacterial or viral intraocular infections. Anterior segment complications included ocular GvHD in 37/135 (27%), consisting of dry eye syndrome in 22 (16%) and conjunctival involvement in 15/135 (11%).

Two patients developed uveitis, both with negative intraocular fluid analyses for infectious agents. The first case of anterior uveitis (0.7%) developed concurrently with an exacerbation of chronic GvHD and diminished quickly with anti-GvHD therapy; in the other case the patient developed uveitis after radiation therapy. Optic disc edema (ODE) was observed in 3 patients (2%) and was associated with the *Scedosporium apiospermum* chorioretinitis in 1 patient. In the second case ODE was accompanied by perimacular puckering OD and was diagnosed using optical coherence tomography (OCT) and fluorescein angiography (FAG). During pars plana vitrectomy (PPV) no infectious agent was found and it was hypothesized that ODE might be related to cyclosporine medication in this patient. The final VA slightly improved and remained stable at VA 0.4. In the third case, the patient's decreasing VA could not be explained by the ophthalmic examination findings. By means of OCT and FAG, ODE and mild unilateral papillitis were diagnosed. The patient developed severe systemic GvHD, successfully treated with high-dose prednisone po. Despite the clinical improvement of optic disc edema, the vision remained very low (VA 0.1). The ODE in this patient was considered idiopathic as we could not identify any cause of ODE by neurologic examination and imaging and the patient did not use cyclosporine medication.

Selected Case Report: Intraocular Infection with *Scedosporium apiospermum*

A 59-year-old female suffered from non-Hodgkin lymphoma for which she underwent myeloablative matched unrelated donor allo-SCT, secondary to total body irradiation and chemotherapy. One year later she was diagnosed with right elbow abscess and showed osteomyelitis signs and subsequently developed *Scedosporium aspiospermum* endocarditis and parieto-occipital abscess in the left hemisphere. Simultaneously, the patient developed painless loss of vision in her right eye and slit-lamp examination revealed normal anterior segment while active chorioretinal lesion was observed during ophthalmoscopy. The *Scedosporium* infection further progressed into a retinal abscess for which she underwent vitrectomy, lensectomy, and retinectomy. The final diagnosis of *Scedosporium apiospermum* chorioretinitis was confirmed from vitreous cultures and the patient was

treated with amfotericine B and voriconazol. Three years later her vision was 0.1 in the affected eye due to inactive retinal scar.

DISCUSSION

Our study documents only 1 case of intraocular infection during a 2-year follow-up of 135 patients after allo-SCT; this infection was caused by the fungus *Scedosporium apiospermum*. Intraocular bacterial and viral infections were not observed, nor was intraocular toxoplasmosis diagnosed. The most frequent ocular sequel of allo-SCT included ocular graft-versus-host disease which developed in 37/135 patients (27%).

Intraocular infections in immunosuppressed patients and their dramatic manifestations may lead to severe visual loss.[5] The prevalence of intraocular infections after solid organ transplants was previously reported to range from 3 up to 15%.[2,6,7] No recent systematic studies are available on the incidence of intraocular infections following allo-SCT. One study reported on a 0.8% incidence of intraocular infections after allo-SCT; however, this study focused mainly on ocular GvHD and furthermore its precise follow-up pattern is not clear.[5] CMV infections after allo-SCT represented the most frequent intraocular infection (2.2%), followed by EBV (2%) and *Toxoplasma gondii* (0.97%).[5,8–12] Originally, intraocular CMV retinitis after allo-SCT was reported to represent a rare complication with low incidence,[13] but Xhaard et al. reported that implementation of mismatched donorship in allo-SCT has increased the CMV retinitis incidence more than 10 times.[11] The reported cases also suffered from chronic GvHD, a disease with a drastically increasing incidence as a result of the matched unrelated donorship techniques.[14] Other reports also suggest that there is a higher chance of CMV infection occurring among CMV seronegative recipients from CMV seropositive donors.[11]

Up-to-date transplantation centers show a great variety of immunosuppressive and antimicrobial regimes in keeping with type, dosage, and duration of the administered medication, resulting in discrepant incidence reports.[4,5,15–17] In our study, we report a single case of disseminated *Scedosporium apiospermum* infection complicated by endocarditis, brain abscess, and chorioretinitis. From a recently conducted literature study such filamentous fungi have been related to poor vision outcomes and low survival rate.[18] Previously, McKelvie et al. described 2 patients with disseminated post-SCT *Scedosporium* sp. endophthalmitis and fungemia, nonresponsive to antifungal therapy with amphotericin B and fluconazole, that resulted in death.[19] Husain et al. conducted a study in which voriconazol was related to a lower mortality rate than amfotericine B or itraconazol.[20] Our patient was successfully treated with a combination of voriconazole and amphotericine B combined with surgical abscess drainage.

Our study reports no intraocular infections due to viruses or bacteria, which is consistent with an earlier report that points out that the major cause of post-transplant systemic infections is due to fungal infections.[15] Although this study was designed in a retrospective fashion, the strict follow-up procedures at the hematology and ophthalmology departments secure a detailed and reliable medical file data collection in regard to complaints registration and detection of intraocular infections. The median follow-up in our study of 15 months allowed an optimal time for intraocular infections to develop, excluding acute retinal necrosis and progressive outer retinal necrosis, which have been documented to develop in most cases later than 5 years after transplantation.[8] In this study, 19 patients had a post-SCT follow-up time longer than 5 years and none of them developed these viral intraocular manifestations.

Our findings of lack of intraocular infections are consistent with a previous, but independently conducted study by Westeneng et al. in the UMCU[21] with a prospectively kept database, in which the incidence of intraocular infection of unknown origin was 1.1%.

Our results point out that when preventive antibacterial and antiviral treatment regimens are combined with regular controls for reactivations of systemic infections and early treatments they effectively decrease the occurrence of intraocular infections. Although the modern prophylactic protocol is successful in reducing the probability of bacterial and viral infections, the awareness of a possible fungal intraocular infection and its timely recognition are of high importance for visual prognosis of post allo-SCT patients.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Funding was provided by Dr. PF Fischer Stichting, Landelijke stichting voor Blinden en Slechtzienden (LSBS), Stichting Nederlands.

Oogheelkundig Onderzoek (SNOO), Stichting Blindenpenning, Gelderse Blinden Stichting, The Netherlands.

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