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Ocular complications in a young pediatric population following bone marrow transplantation

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Abstract

Purpose—To investigate ocular complications associated with bone marrow transplant and associated continued maintenance therapy in a preschool population.

Methods—The medical records of patients <7 years of age were reviewed retrospectively. Patient charts were screened for cataract formation, dry eye, and other anterior and posterior segment disease.

Results—Of 270 cases reviewed, 91 met inclusion criteria. Mean age at diagnosis was 3.17 years. Average follow-up was 5.8 years (range, 1.9 months–14.1 years). Of the 91, 37 patients developed cataracts (35 bilaterally) over a 14-year period. Cumulative incidence corrected for competing event (death before cataract) for the study population was found to be 58.4% after 14 years. Univariate analysis for cataract formation showed statistical significance for total body irradiation dose, age at diagnosis, race, donor type (related vs unrelated), product type, diagnosis type, survival status, calcineurin inhibitor use, and bisulfan, cytarabine, and thiotepe use. Multivariate analysis for competing event (death), showed that total body irradiation dose was not statistically significant; however, when studied in a binary logistic regression model, total body irradiation dose was statistically significant. Notably, steroid use and presence of graft-versus-host disease did not show statistical significance for cataract development. No other ocular complication was found in sufficient quantities to allow statistical analyses.

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Conclusions—Due to the high incidence of cataract formation in this population, especially those enduring a treatment regimen with total body irradiation, we propose screening examinations by a pediatric or general ophthalmologist at least annually. We also urge a low threshold for treatment of dry eye syndrome.

Allogeneic bone marrow transplantation (BMT) has become a widely used treatment for childhood leukemia, myelodysplastic syndrome, lymphoma, solid tumors, and several nonmalignant diseases.¹ Ocular complications following BMT include cataract development and dry eye syndrome. The effects of these ocular complications on patients' quality of life can be significant, especially in children, who are less likely to report symptoms. Young children who have not reached school age are especially vulnerable, because they often have limited verbal skills and may not be able to express their symptoms, and they may not respond to any therapeutic interventions. In addition, young children who become long-term survivors may have to endure these complications for many years.

Most of the published reports describing ocular complications in children following BMT are retrospective and include children of all ages.^{1,2} Studies include both allogeneic and autologous recipients.^{1,2} The present study aimed to analyze the incidence and risk factors for ocular complications following allogeneic BMT in children 6 years of age at the time of transplantation.

Subjects and Methods

This study was approved by the Institutional Review Board of St. Jude Children's Research Hospital and was compliant with the US Health Insurance Portability and Accountability Act of 1996. The medical records of consecutive patients 6 years of age who received allogeneic BMT at St. Jude Children's Research Hospital between 1995 and 2010 were reviewed retrospectively. Patients were included if they had ophthalmic examinations prior to BMT and at least one follow-up examination during the 5 years after transplantation.

Ocular examinations were performed by an ophthalmologist at St. Jude. Examination included visual acuity when permitted by age, biomicroscopic or penlight examination of the anterior segment, and dilated fundus examination. All patients included in the study underwent transplantation according to the treatment protocols used by the Bone Marrow Transplant Department at St. Jude. Pretransplant conditioning regimens were determined by the patients' diagnoses and treatment protocols.

The patient's medical records were screened for development of cataract and dry eye as well as any additional ocular disease as described in the ophthalmologist's examination notes. The following data were collected: patient demographics, diagnosis and treatment protocol, age at transplantation, dose of radiation received (total and dose per fraction), site of irradiation, history of irradiation prior to conditioning therapy, use of calcineurin inhibitors for any reason, chemotherapy used for conditioning, inclusion of steroids in conditioning regimen, presence of acute and chronic graft-versus-host disease (GVHD), pre- and post-transplant ophthalmic examinations, post-transplant ocular complications, post-transplant ocular complaints, and treatment outcomes.

Statistical Analysis

Descriptive statistics were analyzed and compared either by the Pearson χ^2 test or the Fisher exact test for categorical variables, and by a two-sample *t* test or a Wilcoxon rank sum test for quantitative variables based on the normality assumption criteria, respectively. Logistic regression was performed using the ocular complication as binary outcomes, and its association with all other covariates was studied. Overall survival probabilities were estimated using the Kaplan-Meier method and compared using log-rank test. Overall survival was defined as the time from BMT until death from any cause, censoring those alive at the last follow-up. The cumulative incidence of an event was estimated by the Kalbfleisch-Prentice method, and compared using Gray's test.^{3,4} In the estimation of cumulative incidence of development of cataract, deaths due to any cause is considered a competing event. Fine and Gray's regression model was used to evaluate the associations between cumulative incidence and all other covariates listed below. Risk factors considered in univariate analysis included age at transplant, sex, race, presence or absence of cytomegalovirus, diagnosis, dose of radiation received, donor type, site of irradiation, history of irradiation prior to conditioning therapy, treatment, conditioning regimen, inclusion of steroids in conditioning regimen, product type, presence of acute and chronic GVHD, and type of treatment.

The parameters associated with outcomes in univariate analyses at a nominal level of $P=0.15$ were included in their respective multivariate analyses based on a stepwise model selection strategy that used logistic regression and Fine and Gray's regression model. All the reported P values are two-sided and considered significant if <0.05 . Statistical analyses were performed with *SAS* version 9.4 and *R* version 2.13.1.

Results

A total of 270 young children received allogeneic BMT during the study period. Of these, 91 (41 females) met inclusion criteria; 179 patients were excluded because of either a lack of pre-BMT evaluation (33) or lack of follow-up, including 83 that died before they were seen twice in the eye clinic. Sixty-eight patients were white, 13 were African American, and 10 were of other ethnic origins. All patients included in our study received allogeneic BMT. The mean patient age at time of BMT was 3.2 years (range, 0.1-6.99 years). Mean follow-up period was 5.8 years (range, 1.9 months to 14.1 years); median follow-up was 5.25 years. Fourteen of the patients ultimately died during the follow-up period from disease complications.

The most common indications for BMT were acute lymphoblastic leukemia (26 patients) and acute myelogenous leukemia (18 patients). Other indications for BMT are noted in Table 1. Table 2 lists characteristics of the study population.

Seventy-two eyes of 37 patients (41%) patients developed cataracts following BMT; cataracts were bilateral except in all but 2 patients. Of these 37 patients, 8 required cataract surgery. After surgery, 5 patients achieved visual acuities of 20/20 to 20/30; 2 achieved 20/40; and 1 achieved 20/80. Descriptive analysis showed the following variables as significant for development of cataract ($P < 0.05$): older age at diagnosis, unmatched donor,

product type (hemopoietic progenitor cells–marrow), match, survival status, treatment, specific chemotherapy used for conditioning treatment (busulfan, cytarabine, and thiotepea), total body irradiation (TBI) dose, and use of calcineurin inhibitors. Additionally, white race and diagnosis met the threshold for inclusion in the multivariate analyses ($P < 0.15$).

Some underlying disease processes were also associated with higher prevalence of cataract development. For instance, cataract was more likely in patients with hematologic malignancies than in patients with nonhematologic malignancies ($P = 0.06$).

Three particular chemotherapy agents showed statistical significance in the univariate logistic model: busulfan ($P = 0.002$) and thiotepea ($P = 0.02$) were associated with a decreased incidence of cataract formation, whereas cytarabine ($P < 0.0001$) was associated with increased incidence. Busulfan and TBI were the only factors that showed statistical significance in the multivariate analysis (Table 3). The odds ratio of cataract development in a patient treated with busulfan was 0.14 (95% CI, 0.04-0.75).

Survival was a factor in cataract development; therefore, a life table was created to show the increased incidence of cataract development with increasing survival (Figure 1). The cumulative incidence of cataract development considering death (due to any cause) as a competing event was calculated. The incidence of cataract development was 54.2% at 10 years and 58.4% at 14 years.

Fifty-five patients in our study received TBI; of these, 37 developed cataracts. All patients that developed cataracts in our study received TBI. There was no statistical difference in TBI dose between patients that developed cataract and those that did not. There was a statistical difference in follow-up in patients that developed cataract (mean, 10.3 years) versus those that did not (mean, 3.96 years).

No other ocular complication was present in sufficient quantities to allow adequate statistical analyses regarding possible contributing variables. Dry eye syndrome was found in 13 children in our cohort following BMT (none had dry eye syndrome prior to BMT). Dry eye syndrome was diagnosed by either the presence of superficial punctate keratopathy on slit-lamp biomicroscopy (10 patients), or Schirmer's testing (with topical anesthetic) of < 5 mm (2 patients), or both (1 patient). This represents a prevalence of dry eye syndrome of 14.3% in our study population.

Other anterior segment and orbital involvement included 2 patients who developed preseptal cellulitis, 1 patient who acquired significant corneal haze that required penetrating keratoplasty (due to Hurler syndrome), 1 patient who developed Herpes simplex keratitis that was treated with acyclovir, and 1 patient who developed conjunctivitis due to cytarabine.

The neurologic and posterior segment pathology seen in this population included 6 patients with optic nerve atrophy (5 of whom had osteopetrosis) and 2 patients with ocular choroidomas (of whom 1 developed optic atrophy). Finally, one instance of each of the following pathologies was noted in separate patients: retinoblastoma requiring enucleation (this patient, who was negative for the *RB1* mutation, developed acute myelogenous leukemia

(AML) after enucleation and required BMT), presumed ocular histoplasmosis syndrome, atrophic retinal holes, retinal hemorrhage (cytomegalovirus negative), and chorioretinal scar.

Discussion

This study presents a large group of young children who developed ocular complications after undergoing allogeneic BMT. To our knowledge, this is the first study to consider only preschool-aged children following BMT. Our results show that in this age group, the main complication is cataract development, seen in 41% of our patients, including 67% of those who received TBI. The cumulative incidence is 58.4% at the end of 14 years. This finding agrees with previous studies in children and adults following BMT that reported the prevalence of cataracts to vary from 8.5% to 83.3%.^{5,6} Recent data have found a narrowed prevalence of 25%-50% in older study populations.⁷⁻⁹

Of the children who developed cataracts in our study, 22% (9% of the total study population) ultimately required cataract surgery with intraocular lens implantation in both eyes. Similarly, Suh and colleagues¹ (age range, 0.3-18 years at transplantation) and Deeg and colleagues¹⁰ (age range, 1.9-52.1 years at transplantation) reported that 20.8% and 20% of patients, respectively, required cataract surgery after receiving fractionated TBI.^{1,10} Horwitz and colleagues showed that 8.1% of "childhood leukemia survivors" required corrective surgery after BMT.⁷ Like previous authors,^{1,11,12} our visual outcomes after cataract surgery were favorable. Of note, the patient with 20/80 visual acuity was uncooperative with testing. Because one-quarter of the children who developed cataracts in our study required surgery, we feel this necessitates close follow-up, especially in this unique patient population, who are at higher risk for amblyopia.

Ionizing radiation has long been recognized as a risk factor for the development of cataract.¹³ Conditioning with TBI was statistically associated with the cataract development in our study. In fact, cataracts developed only in patients treated with TBI. However, dose was not a factor in cataract development. Additionally, patients with hematological malignancies, who are more likely to receive TBI, were at increased risk of developing cataracts, although it did not achieve statistical significance ($P=0.06$).

The use of fractionated versus unfractionated TBI may play a role in cataract development. Livesey and colleagues⁵ found that the prevalence of cataract after unfractionated TBI was 83.3% in a population of teenage and adult patients who had undergone autologous and allogeneic BMT. They also found that among patients receiving fractionated TBI, none developed cataracts, although the longest follow-up in this group was only 18 months. Deeg and colleagues¹⁴ found that the relative risk of developing cataracts after receiving unfractionated TBI was almost five times greater than after fractionated TBI or no TBI.¹⁴ Our TBI-conditioned patients received fractionated TBI (unfractionated TBI is rarely employed). Our findings that only TBI-conditioned patients (37 of 55) developed cataracts further confirms that ionizing radiation is an important risk factor in cataract development, particularly in this age group.

Notably, some chemotherapy agents showed a statistical significance in our study. Thiotepa and busulfan were associated with decreased risk of cataract formation, whereas cytarabine seemed to be associated with increased risk. Busulfan has been indicated in cataract formation in numerous studies.¹⁵⁻¹⁷ In our study population, however, busulfan was associated with a decreased incidence of cataract formation relative to TBI. A thorough literature search showed no studies linking cytarabine or thiotepa to cataract formation or protection. Cytarabine showed a strong correlation with cataract formation, with an odds ratio of 4.61 (95% CI). The incidence over the 14-year study period for cataract formation in patients taking cytarabine is 78.6%. This may be due to the concurrent use of cytarabine and TBI. To our knowledge, this association between cytarabine and cataract formation has not been shown in the peer-reviewed literature previously. With regard to thiotepa, it is also possible that the significance seen pertains not to the actual agents but to the disease it is used to treat. However, we do not believe this to be the case with cytarabine, because this association showed significance in our multivariate analysis.

Dry eye syndrome occurs in up to 44% of adults who undergo BMT.¹⁸⁻²¹ Unfortunately, we were unable to effectively study contributing factors to dry eye syndrome in young children even though we had a prevalence of 41.4% at 14 years. We agree with Suh and colleagues,¹ who postulated that the difficulties associated with diagnosing the highly subjective elements of dry eye syndrome in preverbal children were a determining factor in his study, which found a 12.5% prevalence in older children (average age, 8.4 years). Therefore, we recommend periodic examinations to evaluate for dry eye symptoms and SPK in order to prevent potential corneal complications from this process.

Although there were relatively few posterior segment complications noted in our study, we recommend baseline ophthalmic examinations prior to BMT to monitor for preexisting pathology and serially while immunosuppressed. If opportunistic infections are found in other organ systems, an eye examination should be part of the patient's work-up. Often children are too young to complain of visual symptoms, and the ocular manifestations of such infections can be devastating.

As expected, all patients with osteopetrosis developed optic nerve atrophy. Therefore, patients with osteopetrosis require closer follow-up, due to their disease and treatment.

Our paper is limited by its retrospective nature and difficulty with obtaining extensive clinical data because of our patients' young age.

Patients with a history of BMT during their preschool years, especially those enduring a treatment regimen with TBI, should be followed by an ophthalmologist with at least yearly appointments for life. We urge ophthalmologists who care for this specific patient population to have a low threshold for topical treatments for dry eye. Posterior segment disease in immunocompromised patients can be devastating, so close monitoring of risk factors for infectious retinitis and changes in vision is encouraged, with increased frequency of dilated examinations recommended for those patients too young to communicate a change in vision. Finally, we also encourage vigilance for the development of cataract in these patients. They should be monitored regularly and treated if there is a risk for amblyopia.

Literature Search

PubMed was searched on September 18, 2017, for English-language results (1981-present) using the following terms: *ocular complications* and *bone marrow transplant*.

References

1. Suh DW, Ruttum MS, Stuckenschneider BJ, Meiler WF, Kilvin JD. Ocular findings after bone marrow transplantation in a pediatric population. *Ophthalmology*. 1999; 106:1564–70. [PubMed: 10442905]
2. De Marco R, Dassio DA, Vittone P. A retrospective study of ocular side effects in children undergoing bone marrow transplantation. *Eur J Ophthalmol*. 1996; 6:436–9. [PubMed: 8997588]
3. Prentice RL, Kalbfleisch JD, Peterson AV Jr, Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks. *Biometrics*. 1978; 34:541–54. [PubMed: 373811]
4. Gray R. A class of k-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat*. 1988; 16:1141–54.
5. Livesey SJ, Holmes JA, Whittaker JA. Ocular complications of bone marrow transplantation. *Eye (Lond)*. 1989; 3:271–6. [PubMed: 2693135]
6. Belkacémi Y, Ozsahin M, Pène F, et al. Cataractogenesis after total body irradiation. *Int J Radiat Oncol Biol Phys*. 1996; 35:53–60. [PubMed: 8641927]
7. Horwitz M, Auquier P, Barlogis V, et al. Incidence and risk factors for cataract after haematopoietic stem cell transplantation for childhood leukaemia: an LEA study. *Brit J Haematol*. 2015; 168:518–25. [PubMed: 25284463]
8. Teär Fahnehjelm K, Törnquist AL, Olsson M, Bäckström I, Andersson Grönlund M, Winiarski J. Cataract after allogeneic hematopoietic stem cell transplantation in childhood. *Acta Paediatrica*. 2016; 105:82–9. [PubMed: 26331596]
9. Madden LM, Ngwube AI, Shenoy S, Druley TE, Hayashi RJ. Late toxicity of a novel allogeneic stem cell transplant using single fraction total body irradiation for hematologic malignancies in children. *J Ped Hematol Oncol*. 2015; 37:e94–101.
10. Deeg HJ, Storb R, Thomas ED. Bone marrow transplantation: a review of delayed complications. *Br J Haematol*. 1984; 57:185–208. [PubMed: 6329256]
11. Calissendorff BM, Bolme P. Cataract development and outcome of surgery in bone marrow transplanted children. *Br J Ophthalmol*. 1993; 77:36–8. [PubMed: 8435397]
12. De Melo Franco R, Kron-Gray MM, De la Parra-Colin P, et al. Outcomes of cataract surgery in graft-versus-host disease. *Cornea*. 2015; 34:506–11. [PubMed: 25826324]
13. Tichelli A. Late ocular complications after bone marrow transplantation. *Nouv Rev Fr Hematol*. 1994; 36:S79–82. [PubMed: 8177722]
14. Deeg HJ, Flournoy N, Sullivan KM, et al. Cataracts after total body irradiation and marrow transplantation: a sparing effect of dose fractionation. *Int J Radiat Oncol Biol Phys*. 1984; 10:957–64. [PubMed: 6378850]
15. Akman N, Avano lu Y, Soysal T. Cataract after busulphan therapy. *Acta Haematol*. 1986; 76:236. [PubMed: 3107313]
16. Ravindranathan MP, Paul VJ, Kuriakose ET. Cataract after busulphan treatment. *Brit Med J*. 1972; 1:218–19. [PubMed: 4500985]
17. Soysal T, Bavuno lu I, Ba lar Z, Aktu lu G. Cataract after prolonged busulphan therapy. *Acta Haematol*. 1993; 90:213. [PubMed: 8140865]
18. Bray LC, Carey PJ, Proctor SJ, Evans RG, Hamilton PJ. Ocular complications of bone marrow transplantation. *Br J Ophthalmol*. 1991; 75:611–14. [PubMed: 1954211]
19. Hirst LW, Jabs DA, Tutschka PJ, Green WR, Santos GW. The eye in bone marrow transplantation. I. Clinical study. *Arch Ophthalmol*. 1983; 101:580–84. [PubMed: 6340648]
20. Jabs DA, Wingard J, Green WR, Farmer ER, Vogelsang G, Saral R. The eye in bone marrow transplantation. III. Conjunctival graft-vs-host disease. *Arch Ophthalmol*. 1989; 107:1343–8. [PubMed: 2675805]

21. Jack MK, Hicks JD. Ocular complications in high-dose chemoradiotherapy and marrow transplantation. *Ann Ophthalmol.* 1981; 13:709–11. [PubMed: 7020552]

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Fig 1.
Cumulative incidence for cataract development considering death due to any cause as competing event.

Table 1
Indications for bone marrow transplant from our study population other than the two most common indications (acute lymphoblastic leukemia and acute myelogenous leukemia)

Other indications for bone marrow transplant
Acute erythroleukemia
Aplastic anemia
Chediak-Higashi disease
Chronic myelogenous leukemia
Dyskeratosis
Ganglioneuroblastoma
Glanzman disease [thrombasthenia]
Granulomatous disease
Histiocytosis X
Hurler syndrome
Hypoplastic anemia, congenital
Juvenile myelomonocytic leukemia
Lymphohistiocytosis
Myelodysplastic syndrome
Osteogenesis imperfecta
Osteopetrosis
Severe combined immunodeficiency syndrome
Sickle cell disease
Wiscott-Aldrich syndrome

Table 2**Patient characteristics**

Characteristic	Frequency	Percentage
Diagnosis		
Hematologic malignancy	58	63.7
Other	33	36.3
Donor type		
Related	46	50.5
Unrelated	45	49.5
Stem cell source		
Peripheral blood/stem cell	20	22
Cord blood	1	1.1
Bone marrow	70	76.9
Match (human leukocyte antigen)		
3/6	12	13.2
4/6	7	7.7
5/6	16	17.6
6/6	56	61.5
Survival status		
Alive	77	84.6
Expired	14	15.4
Treatment		
Radiation + chemotherapy	55	60.4
Chemotherapy only	36	39.6
Received steroids during conditioning	19	20.9
Developed acute graft-vs-host disease	43	47.3
Developed chronic graft-vs-host disease	7	7.7
Developed any graft-vs-host disease	43	47.3
Total body irradiation	55	60.4

Table 3
Univariate and multivariate logistic regression analysis for development of cataract

Variable	Category	Univariate analysis	
		OR (95% CI)	P value ^a
Age at diagnosis		1.182 (0.952-1.467)	0.1299
Age at transplant		1.071 (0.867-1.322)	0.5272
TBI dose (quantitative)		1.003 (0.999-1.007)	0.1171
Head dose (quantitative)		1.002 (0.995-1.009)	0.6175
Dose on other sites (quantitative)		1.137 (0.002-769.5)	0.9691
Sex	Male vs female	1.362 (0.584-3.174)	0.4742
Race			0.1159
	White vs black	2.963 (0.749-11.72)	0.0385
	Other vs black	0.833 (0.111-6.259)	0.4016
Donor type	Unrelated vs related	2.901 (1.217-6.917)	0.0163
Product type (hematopoietic progenitor cells)			0.0194
	Cord vs apheresis	0.000 (0.000 to >999.99)	0.9708
	Marrow vs apheresis	9.000 (1.941-41.74)	0.9614
Diagnosis category (type of malignancy)			0.0624
	Myeloid vs lymphoid	1.000 (0.355-2.815)	0.2080
	Others vs lymphoid	0.320 (0.106-0.968)	0.0187
Match x/6			0.1187
	4/6 vs 3/6	4.400 (0.319-60.61)	0.8891
	5/6 vs 3/6	14.14 (1.457-137.3)	0.0355
	6/6 vs 3/6	8.871 (1.071-73.45)	0.1409
Steroids	Yes vs no	0.610 (0.209-1.787)	0.3677
Survival status	Expired vs alive	0.088 (0.011-0.703)	0.0219
Treatment	Radiation + chemotherapy vs chemotherapy	>999.9 (<0.001 to >999.9)	0.9425
Acute graft-vs-host disease	Yes vs no	1.099 (0.476-2.540)	0.8253
Chronic graft-vs-host disease	Yes vs no	0.560 (0.103-3.054)	0.5031
Any graft-vs-host disease	Yes vs no	1.099 (0.476-2.540)	0.8253
CNI	Yes vs no	6.152 (1.667-22.71)	0.0064
Busulfan ^b	Yes vs no	0.139 (0.038-0.509)	0.0029
Campath	Yes vs no	0.000 (0.000 to <0.001)	0.9807
Carboplatin	Yes vs no	0.000 (0.000 to <0.001)	0.9864
Cyclophosphamide	Yes vs no	>999.99 (<0.001 to >999.99)	0.9423
Cytarabine	Yes vs no	11.73 (4.013-34.30)	<0.0001
Etoposide	Yes vs no	0.000 (0.000 to >999.999)	0.9664
Fludarabine	Yes vs no	0.000 (0.000 to >999.999)	0.9442
Melphalan	Yes vs no	0.000 (0.000 to >999.999)	0.9405
Thiotepa	Yes vs no	0.314 (0.118-0.841)	0.0212
Total body irradiation ^c	Yes vs no	11.43 (4.202-31.10)	<0.0001

^a A P value of <0.05 was considered significant.

^bSignificant on multivariate analysis: OR = 0.180; 95% CI, 0.043-0.752; $P=0.02$.

^cSignificant on multivariate analysis: OR = 9.992; 95% CI, 3.535-28.240; $P<0.0001$.

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