CENTRAL CORNEAL OPACIFICATION RESULTING FROM RECENT CHEMOTHERAPY IN CORNEAL DONORS

BY **Woodford S. Van Meter MD***

ABSTRACT

Purpose: Ocular surface disease following penetrating keratoplasty has been shown to increase patient morbidity and adversely affect graft survival. Five cases of dense central subepithelial opacification were noted in keratoplasty patients who received tissue from donors who had chemotherapy prior to death. Cancer-related deaths account for approximately 20% of the cornea donor pool. The purpose of this study was to identify the effect of recent systemic antimetabolite therapy on donor corneas.

Methods: Eye bank donor charts of 120 consecutive penetrating keratoplasty donors were retrospectively reviewed for cancer-related deaths. Donors who received chemotherapy prior to death were identified. Recipient records of those patients receiving tissue from donors that had recently undergone systemic chemotherapy were reviewed. Corneal clarity and postoperative ocular surface disease were noted by the surgeon.

Results: Twenty-nine of 120 cornea donors (24%) had a cancer-related cause of death. Five of these 29 donors (17%) had undergone systemic chemotherapy with antimetabolite drugs (which inhibit microtubule formation) within the previous 8 weeks. All 5 recipients postoperatively developed central subepithelial opacification in spite of temporary tarsorrhaphy performed at the time of keratoplasty. Central corneal opacification was severe enough in 3 patients to require regrafting for visual improvement. Histopathology showed abnormality of the central epithelial basement membrane, apoptosis of basal epithelial cells, and thinning of the epithelial cell layer.

Conclusion: Corneas from donors who received a full course of recent systemic antimetabolite therapy are associated with central subepithelial scarring following keratoplasty. Corneal surgeons should be aware of the potential for severe ocular surface disease when using donor tissue from patients with metastatic cancer.

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INTRODUCTION

Corneal surface disease is one of many variables affecting the quality of the postkeratoplasty donor cornea. Chronic ocular surface disease has been shown to cause significant morbidity, delay visual rehabilitation, result in scarring of the anterior stroma, and reduce visual acuity in patients following penetrating keratoplasty.[1] Decreased visual acuity may result from a poor corneal surface due to an irregular tear film, permanent damage to Bowman's layer, and scarring of the anterior stroma. Epitheliopathy in different patterns, such as whorl, vortex, and superficial punctate keratopathy, have previously been described.[2-4] Stulting and colleagues[5] noted in 1988 that the overall corneal graft failure rate in patients with the epithelium removed at the time of surgery was higher than in patients with an intact epithelium. Price and colleagues[6] estimated that as many as 25% of grafts may fail on account of ocular surface disease.

Multiple factors relating to the donor and the host influence the clarity of the donor cornea. Prolonged death-to-preservation time in donor corneas is more likely to result in epitheliopathy in the recipient graft. Mannis and associates in 1997 noted that recipient patient factors such as eyelid malposition, abnormal blink, and ocular surface disease affect the success of the transplant.[7,8] Experienced surgeons recognize that an intact epithelium on day 1 predisposes the patient to a smoother postoperative course for the graft, especially in high-risk recipients taking multiple topical medications who may also have dry eyes, ocular surface disease, or exposure problems.

This study reports 5 cases of dense central subepithelial scarring in corneal recipients who received tissue from donors who had completed a course of systemic chemotherapy in the months prior to donation. All 5 donors died of metastatic epithelial tumors (breast, lung, and pancreas) and prior to death had received a full course of antimetabolite treatment to ameliorate their disease

The purpose of this study was to evaluate the connection between recent chemotherapy in the donor and postkeratoplasty surface disease in the recipient cornea. This study was initiated when patients who were noted to have severe central ocular surface disease with central opacification of Bowman's layer, which impaired visual acuity, were anecdotally found to have received donor corneas from patients with cancer-related deaths who had recently undergone systemic chemotherapy with antimetabolite agents (Figure 1). The study sought to identify the effects of systemic chemotherapy in the donor that might contribute to an adverse result in the recipient.

METHODS

One hundred and twenty consecutive donor charts were reviewed from July 2003 through July 2006. All consecutive charts were for donors used by a single surgeon (W.S.V.) for penetrating keratoplasty. Twenty-nine (24%) of these donors had cancer-related causes of death.

Seven of 29 donors had a history recent systemic chemotherapy. A more detailed review of these 7 hospital records showed that 1 patient had recently received a Groshong catheter and died shortly after the advent of chemotherapy. Another patient, who had throat

From the Department of Ophthalmology and Visual Sciences, University of Kentucky College of Medicine, Lexington.
*Presenter.
Bold type indicates AOS member.

cancer, received local injection of chemotherapy that was not systemically administered. Contact was made with the treating physician in the treating institution to establish the regimen of chemotherapy delivered.

Charts of the patients who received tissue from the 7 donors who had undergone chemotherapy were then reviewed for corresponding ocular surface disease. These data comprise the substance of this study. Epitheliopathy, epithelial defects, and central corneal opacification were recorded by one observer (W.S.V.). All keratoplasty patients in the author's practice receive a tarsorrhaphy at the time of surgery. The tarsorrhaphy ordinarily is removed in 3 to 7 days. Patients were seen at 1-month intervals following surgery up to 6 months.

The specific type of cancer and chemotherapy regimen were rarely specified in the donor records. Pertinent hospital and clinic records of the donor were obtained where possible, or the treating physician was interviewed, to establish the type and extent of chemotherapy delivered.

RESULTS

Twenty-nine of 120 donor cornea charts (24%) specified cancer as a primary cause of death. Seven of 29 patients with cancer-related deaths were identified by donor medical record review to have received chemotherapy. One patient (patient 2) received chemotherapy for squamous cell carcinoma in the throat, in which case the chemotherapy was given via catheter through regional arterial administration. Another (patient 6) had a central line catheter inserted for chemotherapy but died shortly after outpatient administration of chemotherapy started. Five donors completed chemotherapy for metastatic tumors of epithelial origin, the results of which are noted in Table 1.

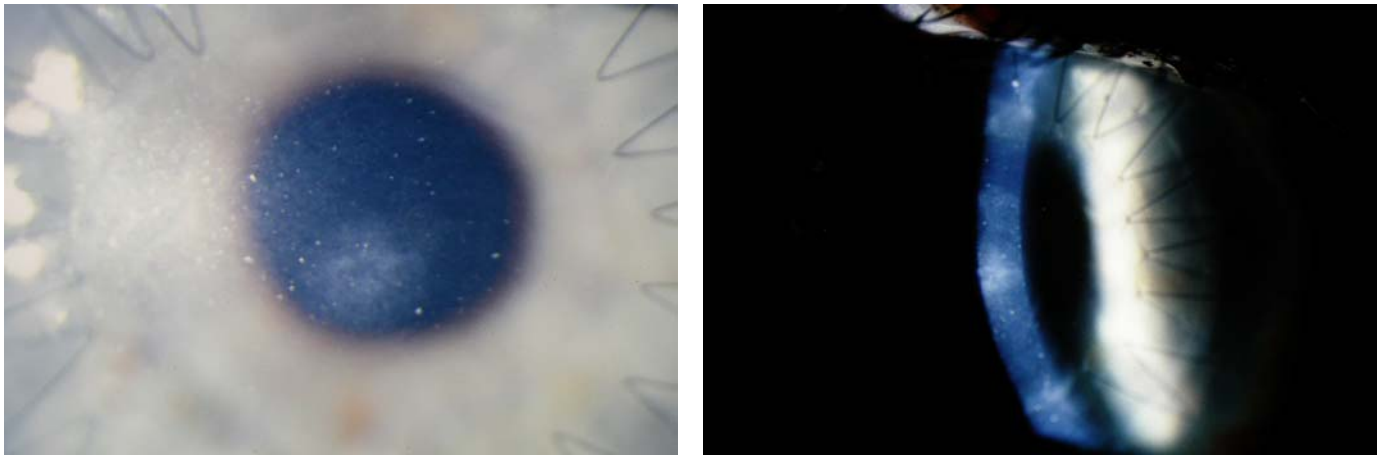

FIGURE 1

Slit-lamp photograph of central corneal opacification with white haze from subepithelial scarring covering pupil in patient 4.

TABLE 1. INFORMATION ON CORNEA DONORS WHO DIED OF CANCER

CASE	DONOR AGE	DEATH-TO-PRESERVATION TIME, hr	CAUSE OF DEATH	CHEMOTHERAPY DRUGS	COMMENTS
1	52	6	Lung CA	Unknown	…
2	52	4	Squamous cell CA, throat	Carboplatin, taxol	Regional administration
3	48	6	Lung CA with liver mets	Carboplatin, cisplatin, taxol	…
4	64	6	Breast CA	Unknown	…
5	59	6	Pancreatic CA	5-Fu, gemcitabine, radiation	…
6	60	9	Small cell lung CA	Carboplatin, etoposide	Groshong catheter recently placed, patient died
7	61	3	Lung CA	Unknown	…

CA, carcinoma.

Office charts of the 7 recipients who received donor tissue from patients who underwent chemotherapy were carefully reviewed for evidence of ocular surface disease (Table 2). All 5 patients who received recipient corneas from patients who had completed systemic chemotherapy developed central 2-mm subepithelial opacities, all of which contributed to decreased vision and impaired funduscopic detail (Figure 2). Although all 5 patients were aware of cloudy vision due to the corneal opacification, 3 patients had sufficient opacification to justify regrafting. The remaining 2 patients did not receive a regraft because of limited visual potential in one and poor physical health in the other.

TABLE 2. INFORMATION ON RECIPIENTS OF DONOR CORNEAS

CASE	GRAFT	DIAGNOSIS	STATUS	COMMENT
1	11/9/03	Fuchs	Central scar	Regrafted
2	4/18/04	Corneal edema	Central SPK	Clear
3	11/17/04	Failed graft	SPK, failed	Regrafted
4	7/7/05	Fuchs	Central scar	Regrafted
5	10/24/05	Central scar	Central scar	2nd PK of case 1
6	1/27/06	Corneal edema	Clear	Clear
	4/27/06	Corneal edema	Central scar	Decreased acuity

PK, penetrating keratoplasty; SPK, superficial punctate keratopathy.

Histopathology of all 3 corneas that were regrafted showed marked irregularity of the central corneal epithelial basement membrane. Apoptosis of basal epithelial cells, thinning of the epithelial cell layer, and anterior stromal changes were also noted (Table 3, Figures 3 and 4). These changes were nonspecific but showed evidence of poor wound healing, poor-quality epithelium, and chronic disruption of normal epithelial basement membrane histology, which occurred in the visual axis.

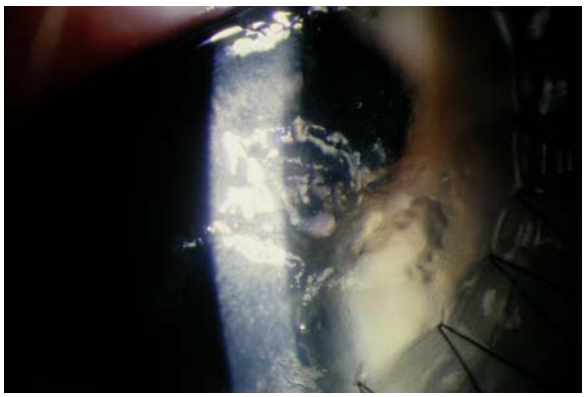

FIGURE 2

Opacification and rough epithelium in central cornea of patient 7.

TABLE 3. HISTOPATHOLOGIC FINDINGS IN THREE PATIENTS WHO HAD CORNEAL REGRAFTING

CASE	FINDINGS
1 (see Figure 3)	Epithelial thickening pannus between basal epithelial and Bowman's layer folds on Bowman's lower edema
3 (see Figure 4)	Epithelial thickening, irregular in Bowman's layer
4 (see Figure 5)	Variable thickness of epithelium Subepithelial pannus

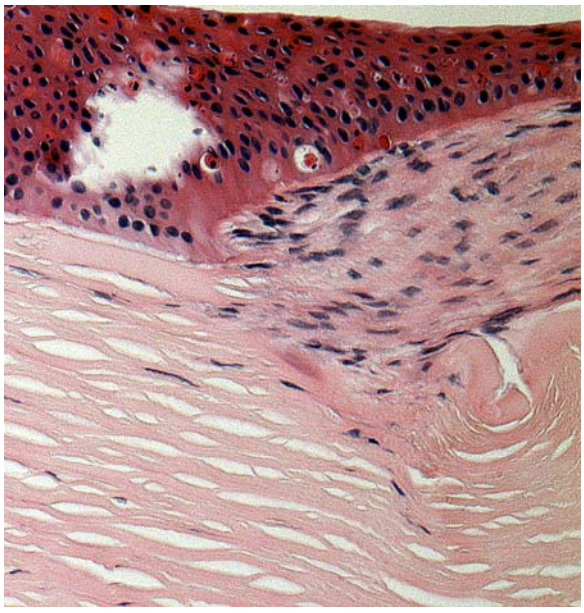

FIGURE 3

Histopathological cross-section of cornea following regraft for central opacification showing apoptosis of central epithelial cells, thickening of Bowman's layer, and varibility of epithelial cell layer thickness in patient 1 (hematoxylin-eosin, ×60).

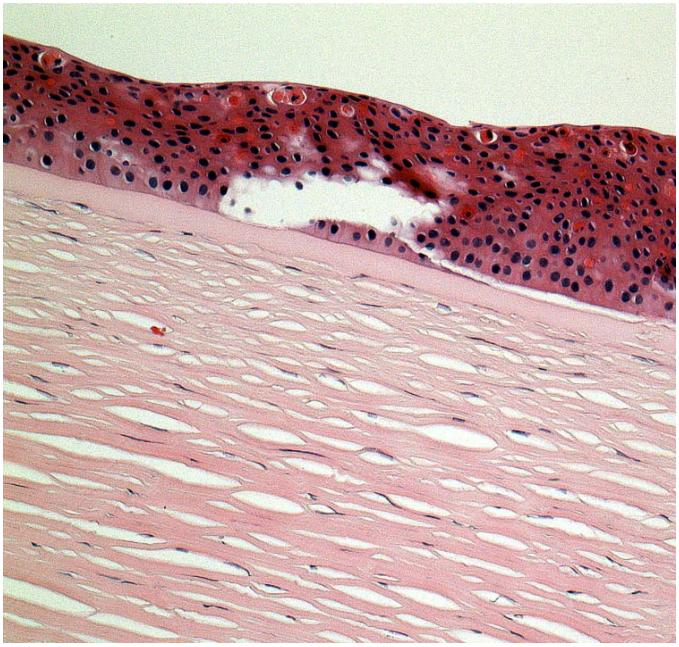

FIGURE 4

Histopathological section showing thickening of Bowman's layer and apoptosis of basal epithelial cells in patient 3 (hematoxylin-eosin, ×60).

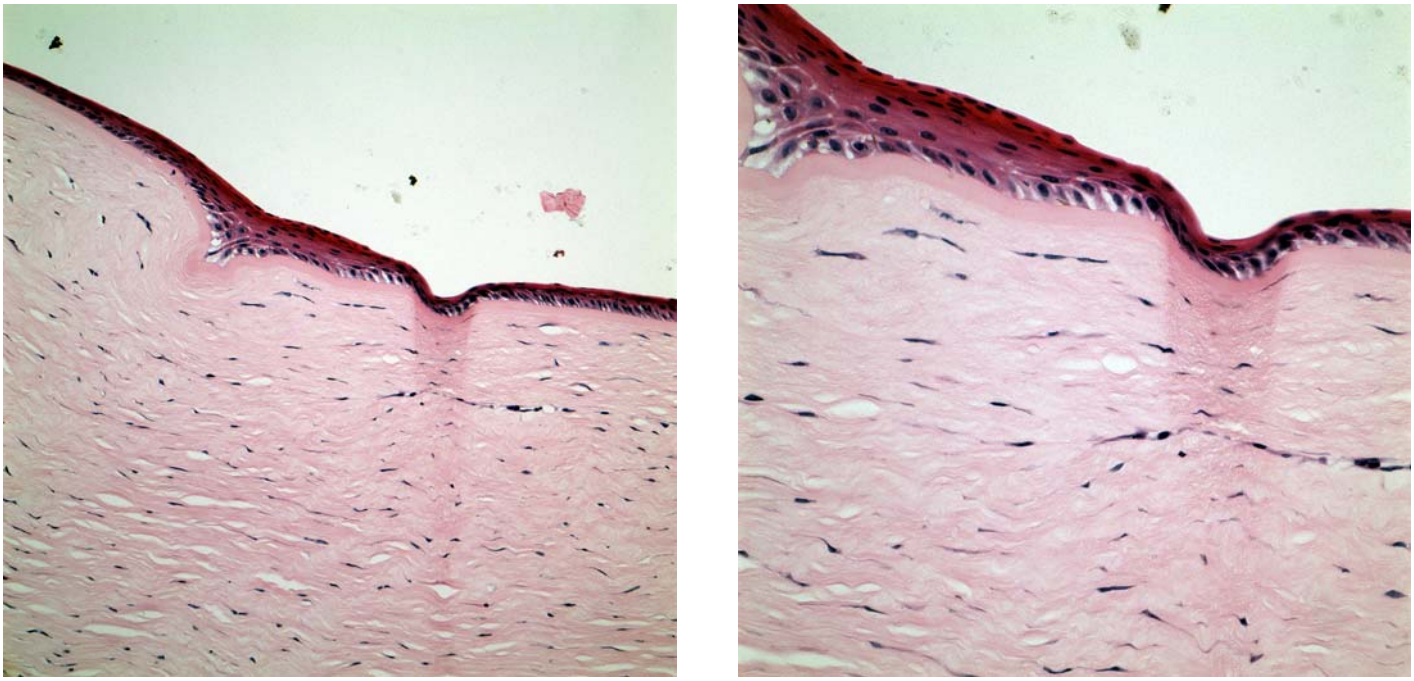

FIGURE 5

Histopathological sections showing variable thickness of the epithelium with a subepithelial pannus in patient 4 (hematoxylin-eosin, ×20).

DISCUSSION

The dense central subepithelial scarring noted in 5 recipient patients is presumed to be due to systemic chemotherapy administered to donor patients within the past few months prior to death. Donor tissue from the 5 patients who completed chemotherapy within the months prior to donation had severe wound healing problems in the immediate postoperative period, even with a temporary tarsorrhaphy placed at the time of keratoplasty. Although multiple other factors, such as death-to-preservation interval, exposure prior to harvesting, and recipient eyelid conditions, can cause postkeratoplasty ocular surface disease, the density of the scarring and central

corneal location were more severe than that usually seen in chronic ocular surface disease. The circular shape of the opacity was unlike the elliptical shape usually related to eyelid pathology or exposure.

Histopathology of the central corneal opacity from 3 of the 5 patients showed thinning of the epithelial basement membrane, thinning of the epithelial cell layer, and apoptosis of epithelial cells. Such changes in the Bowman's layer are nonspecific but indicated damage of the epithelial basement membrane. In all 5 patients, the damage is due in part from the effect of alkylating agents in the corneal tear film on the corneal epithelium. Such changes are consistent with clinical findings in patients receiving systemic alkylating agents who complain of photophobia, foreign body sensation, pain, and tearing due to corneal epitheliopathy. These patients frequently have a normal Schirmer test but inhibited epithelial cell mitosis.

The chemotherapeutic agents used, listed in Table 1, are alkylating agents, which are cell-cycle specific inhibitors of cell replication. Taxol is a natural derivative of the ewe plant, and taxoferol is a synthetic form of taxol. Cisplatin and carboplatin are platinum derivatives that also affect cell division by inhibiting microtubule formation. Microtubule formation is important in the spread of new epithelial cells onto the donor cornea basement membrane substrate and, not surprisingly, would be adversely affected by any material that impairs microtubules. Platinum is also an intercalating agent that interferes with DNA synthesis. 5-Fu is an antimetabolite that predominately cross-binds and inhibits DNA synthesis by interfering with the f-dump enzyme. The specific mechanism of action of gemcitabine is unknown, although this drug is said to facilitate DNA breakage. The relative doses, length of time, and cycles of chemotherapy vary tremendously with different protocols for each patient, based on diagnosis, age, and extent of spread. The effect of specific antimetabolites on a patient's precorneal tear film is dose-related and can depend on host factors, such as age, eyelid condition, topical medications, and corneal health, all of which are important determinants of corneal epithelial wound healing in general.

According to the Eye Bank Association of America (EBAA),[9] 19.2% of cornea donors in 2005 and 2006 died of cancer. In this study 24% of donors died of cancer. Five of 29 patients (17%) whose deaths were cancer-related and 4% of all donors in EBAA's series had central opacification of sufficient magnitude to cause an objective and subjective decrease in visual acuity. In 2006, there were 38,784 donors who donated 45,055 globes in EBAA eye banks[9]; 38,784 corneas were utilized for penetrating keratoplasty.[9] The potential effect of chemotherapy in donors on postoperative ocular surface disease, extrapolated nationally based on the numbers in this study, is that 4% of 38,784 recipients, or 1551 keratoplasty patients, might be susceptible to severe ocular surface disease due to chemotherapy in donors.

The significance of these findings is important in the selection of donor tissue. Patients with preexisting ocular surface disease or known eyelid abnormalities would be well advised to start with a healthy cornea epithelium. Tissue from patients with recent antimetabolite therapy may be contraindicated in elderly patients with dry eyes. However, this tissue exposed to antimetabolites would seem well suited for endothelial keratoplasty, where the endothelium is transplanted but not the anterior stroma.

More problematic is the question of how to obtain reliable information on potential cornea donors who have had recent chemotherapy in a timely fashion following consent for donation. The extensive research required to find medical records on donors with cancer-related deaths is not always possible, even by motivated eye bank personnel. The families of patients who may have had chemotherapy months before might not understand the relevance of previous treatment in the context of the deteriorating medical condition of a loved one. Chemotherapy that may have been started and abruptly terminated due to a variety of conditions, or chemotherapy administered for local rather than systemic disease, may not affect the donor corneal epithelium, as noted in patients 2 and 6 in Table 2.

There were 4 problems with gathering of information in this study. (1) It was difficult to find relevant medical records of the donor in many cases. Treatment was often administered in different locations than the place of death, sometimes months in the past, and often as outpatient therapy. Bereaved families may not recall pertinent details of treatment or even whether the patient received treatment. (2) Information on the mates of the corneas that required regrafting would have been helpful, but we were unable to get reliable information from other practices to establish similar findings in paired donor corneas. (3) The variability of chemotherapy is extraordinary enough to preclude the exact mechanism of action of central corneal opacification noted in these patients. Different protocols, based loosely on patient age, tumor type, disease stage, tumor grade, patient health, and geographic location, are hard to standardize in any meaningful prospective study in oncology or ophthalmology. (4) The clinical relevance of central opacification due to chemotherapy in cornea donors depends on multiple other host factors, such as eyelid disease, dry eyes, existing ocular inflammation, and the visual needs of the patient.

Corneal transplant surgeons should be aware of the potential for surface disease in patients who receive tissue from donors with metastasis cancer. The projected scarcity of donor tissue in the future, the relative infrequency of significant epitheliopathy related to chemotherapy, and the increasing use of lamellar tissue for endothelial keratoplasty may obviate this problem in the future. However, with the projections of increased cancer deaths in the future, both eye banks and cornea surgeons should recognize the potential for this complication in donor tissue from patients who had recent chemotherapy.

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PEER DISCUSSION

DR JAMES CHODOSH: The Eye Bank Association of America criteria to determine suitability of corneal donors for transplantation has evolved along with emerging pathogens and new diagnostic entities that would make tissue unsuitable or dangerous to the recipient. In the United States, corneal donors are rejected for many reasons, including death due to unknown causes; Creutzfeldt-Jakob disease (in the donor or donor's family member); neurologic disease of unestablished diagnosis; dementia not due to cerebrovascular disease, brain tumor, or head trauma; subacute sclerosing panencephalitis; progressive multifocal leukoencephalopathy; congenital rubella; Reye's syndrome; active viral encephalitis; encephalitis of unknown origin; progressive encephalopathy; active septicemia; active bacterial or fungal endocarditis; active viral hepatitis; rabies; leukemia; active disseminated lymphoma; hepatitis B surface antigen positive; recipient of human pituitary-derived growth hormone from 1963-1985; human T-lymphotropic virus 1 or 2 infection; recipient of dura mater graft; hepatitis C seropositive; HIV positive or at "high risk" for HIV infection. Corneas are considered unsuitable for transplantation when from eyes with retinoblastoma, malignant anterior segment tumors, adenocarcinoma of primary or metastatic origin, active ocular surface or intraocular inflammation, congenital or acquired disorders of the cornea that would preclude a successful outcome (scar, pterygium, ectasia), and prior refractive corneal surgery.[1] These exclusions can be grouped into those that serve to limit the possibility of systemic or local infection of the recipient, those that avoid direct transmission of tumor cells into the recipient eye, and those that ensure corneal clarity and health in the recipient. Systemic chemotherapy for malignancy does not adversely affect corneal endothelial cell counts.[2] Malignancies other than leukemia, disseminated lymphoma, retinoblastoma, ocular adenocarcinoma, or anterior segment tumors have not been considered a contraindication to corneal donation.

In this study, Dr Van Meter has focused our attention on a potential new problem, specifically the transplantation of corneas from deceased donors who have received systemic chemotherapy for cancer. Out of 120 consecutive corneal transplants, 29 donor charts (24%) specified cancer as the primary cause of death, and 5 of these had received systemic chemotherapy at some time prior to the donor's death. The 5 recipients of these corneas all developed central subepithelial scars following prolonged epitheliopathy in the donor, and 3 required regraft. In the 3 corneas that were removed for regrafting, Van Meter further reports abnormal corneal epithelial basement membrane, thinning of the epithelial cell layer, and apoptosis of basal epithelial cells.

There are questions about the submitted manuscript that deserve mention. How many of the 91 corneal donors for which cancer was not listed as the primary cause of death actually had cancer and also received chemotherapy? What was the rate of similar corneal opacity in corneal recipients from donors not known to have received chemotherapy? What was the time from last administration of chemotherapy to death of the donors? Did some donors receive systemic chemotherapeutic agents not listed by Van Meter that did not develop corneal opacities? Van Meter describes apoptosis of basal epithelial cells in the 3 removed corneas. However, apoptosis cannot be determined reliably by histopathology. TUNEL (terminal transferase dUTP nick end labeling) assay would be a more appropriate method for detecting DNA fragmentation, with appropriate controls to include corneas removed for other indications. Finally, institutional review board approval for the study was not discussed in the submitted manuscript. The inclusion of corneal donation numbers and recipient initials is unnecessary and could violate the confidentiality of health-related information for both donor and recipient.

If confirmed, Van Meter's results have important implications. Malignancy is the primary cause of one-fourth of all deaths in the United States and is the second leading cause of death after heart disease.[3] However, the death certificate is a less-than-perfect instrument to identify potential donors who might have received systemic chemotherapy. When one includes deaths in individuals with malignancy but with another cause of death on their death certificate, the number of affected donors would be significant. Further complicating matters, up to one-third of individuals may not recall having cancer on simple surveys[4] and may not have reported their prior cancer on their admission to a hospital. A careful case-control study could determine whether a true association exists between recent systemic chemotherapy in the corneal donor and subsequent poor outcome of keratoplasty in the corneal recipient.

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DR. VERINDER S. NIRANKARI: Most interesting paper, Woody. We know that in most corneal transplants the epithelium either does not survive long-term storage, or even if it does the donor epithelium is gradually replaced by the host epithelium. If you believe that this is an important problem in patients with recent chemotherapy, then have you considered removing the donor corneal epithelium before performing transplant so that you will not have this problem of donor epithelium causing surface disease? If these patients developed this condition, presumably from the donor epithelium that survived, have you considered removing the epithelium at that stage? If the scarring was superficial, then would you consider performing a lamellar keratectomy rather than a repeat graft?

DR. RALPH C. EAGLE, JR.: How representative are your photomicrographs? I would say that the epithelium appeared two or three or perhaps four times the normal thickness in the images that I saw. In my experience, one frequently observes such individual, presumably apoptotic, cells. I do not know if Hans can speak to that issue, too. This is a very common observation when the corneal epithelium is very thick.

DR. WOODFORD S. VAN METER: I appreciate the primary review of Dr. Chodosh. I do not know how many of the 91 patients did not have cancer, and I am not sure how we can find that information. As I said, this series exposed a real dearth of information on the corneas that we are using for keratoplasty. The medical information on the donors is collected by eye bank personnel. They frequently work late at night, and as you know there is a lot of delegation. Even though I am the medical director, it is neither me nor the executive director who reviews the medical records, but the available technician who can be sent out to harvest the tissue. Treatment for these patients is often administered elsewhere, and frequently the patients go from one place to another to be treated and then return to their home to die. It is difficult to say how many other patients had cancer. You can assume it is more than 29, and certainly some of these 91 non cancer patients might have had cancer or chemotherapy administered. How many of the eyes in the 91 patients without cancer had subsequent corneal opacities? The answer in this particular series was "0". I perform a tarsorrhaphy at the time of surgery, which is probably overkill, but I am particularly interested in postoperative corneal health. What stimulated my curiosity was the unique type of corneal opacity I had observed in these patients. The central opacity frequently seen with lid exposure or dry eyes is more elliptical or linear and is related to where the lids meet. The peculiar round central opacity reported here is clearly unique to the corneal transplant in these patients, since it occurred in the center of the donor epithelium. I appreciate your comments on the temporal sequence of chemotherapy regarding when the opacity developed; however, this is really hard to document and to comment on postoperative patients.

Veri, you are exactly right about the donor corneal epithelium being replaced by the host epithelium and this seems to be a problem within Bowman's layer. The unique features of this opacity are what interested me in trying to determine if I could identify anything on review of the histopathology. Dr. Richard Kielar, our ocular pathologist, said this was a nonspecific finding. I did remove the corneal epithelium by scraping in one patient however; scraping really did not affect the size or density of the opacity. I think the opacity is located in Bowman's layer and more deeply than just in the epithelial cells. I do not believe that the donor epithelium contains the noxious stimuli. I believe that a change of the basement membrane affects the resurfacing of the cornea by the host epithelial cells. Presumably some chemotherapy agents may be stored in Bowman's layer; however, I do not know if that is possible. It would be interesting to determine the level of type 4 collagen in this opacity to understand if it is derived from host or donor cells. I agree with all the other comments. This is an early study and we do not have that much additional information except for these few patients. I appreciate all prior comments and hope we can learn more about this clinical picture in the future.