

OHTAC Recommendation

Limbal Stem Cell Transplantation

June 2008

Limbal Stem Cell Transplantation

Issue Background

The Ontario Health Technology Committee (OHTAC) met on May 30, 2008 to review the effectiveness and safety of limbal stem cell transplantation (LSCT) for the treatment of limbal stem cell deficiency (LSCD), based on an evidence based review produced by the Medical Advisory Secretariat.

Limbal stem cell transplantation is a procedure in which limbal stem cells from a donor eye are transplanted into a recipient eye to replenish its depleted limbal stem cell population.

The cornea is covered with a layer of epithelial cells that are generated by stem cells in the limbal area of the eye. When the stem cells are depleted or destroyed, limbal stem cell deficiency (LSCD) develops. In LSCD, the cornea's normal epithelium is replaced with abnormal conjunctival cells and scar tissue resulting in symptoms including pain and severely decreased vision.

A variety of underlying conditions can cause LSCD such as chemical and thermal ocular burns, ultraviolet and ionizing radiation, contact lens wear, microbial infection, Stevens-Johnson Syndrome, and aniridia. Localized LSCD caused by ultraviolet light damage to the limbal stem cells can result in pterygium, a condition characterized by abnormal tissue growth in an eye that may extend onto the cornea.

The incidence and prevalence of non-ptyerygium LSCD in Ontario is not known, but the condition is uncommon. The prevalence of pterygium varies by geographic location with high rates in areas 30 degrees north and south of the equator (the pterygium belt) and lower rates elsewhere. In urban, temperate climates, about 1.2% of Caucasians have pterygium.

Treatment Options for Non-Pterygium Limbal Stem Cell Deficiency

Treatment options available to patients with LSCD include bandage contact lenses, serum drops, and mechanical removal of the abnormal tissue. However, these are disease management options and not curative. Most common ophthalmologic treatments, such as corneal transplants, are not adequate for patients with LSCD because these treatments replace only the epithelial cells, so the symptoms of LSCD return after the limited dividing capability of these cells are exhausted.

Thus, the primary aim of treatment is to replace the limbal stem cell population. Four LSCT procedures have been developed: conjunctival-limbal autologous (CLAU) transplantation; living-related conjunctival-limbal (lr-CLAL) allogeneic transplantation; keratolimbal (KLAL) allogeneic transplantation; and ex vivo expansion of limbal stem cells transplantation. In these procedures, limbal stem cells are removed from a donor eye (the patient's healthy eye or a living-related or cadaver donor eye) and transplanted into the diseased eye. Transplantation of oral mucosal cells (characteristically similar to corneal epithelial cells) has been proposed as a treatment option, but this procedure is investigational.

Treatment Options for Pterygium

The primary treatment for pterygium is surgical removal. However, recurrence rates after simple excision are high: reported recurrence rates range from 24 to 89%. A number of adjuvant therapies are used to reduce the risk of recurrence including conjunctival transplants, amniotic membrane transplants, Mitomycin C (an anti-metabolite drug), and LSCT.

Limbal Stem Cell Transplantation

OHTAC Findings

The Medical Advisory Secretariat systematically reviewed the literature to assess the effectiveness and safety of LSCT for the treatment of patients with LSCD and pterygium. Ten case series examining LSCT for the treatment of non-ptyerygium LSCD and 6 randomized controlled trials examining LSCT as an adjuvant therapy to excision were identified and included in the analysis.

Non-Pterygium Limbal Stem Cell Deficiency

Patients who received CLAU transplants achieved significantly better long-term corneal surface results compared to patients who received allogeneic transplants. There was no significant difference in corneal surface outcomes between the allogeneic transplant options, Ir-CLAL and KLAL. Regardless of graft type, patients with Stevens-Johnson Syndrome had poorer long-term corneal surface outcomes. Similarly, concurrent amniotic membrane transplantation was associated with poorer long-term corneal surface improvements. When the effect of the amniotic membrane was removed, the difference between autologous and allogeneic transplants was much smaller.

No donor eye complications were observed. However, recipient eye complications that could lead to graft failure (epithelial rejection, microbial keratitis, and corneal ulceration) occurred in 6 to 16% of patients.

Patients who received CLAU transplants had a significantly higher rate of visual acuity improvement compared with those who received Ir-CLAL transplants. However, patients with deep corneal scarring will require a corneal transplant several months after the LSCT to achieve adequate improvements in vision.

Therefore, there is very low-quality evidence that LSCT results in corneal re-epithelialization and improved vision in patients with LSCD, but patients who receive concurrent amniotic membrane transplants have poorer outcomes. Conjunctival-limbal autologous transplantation is the treatment option of choice, but if it is not possible, Ir-CLAL or KLAL allogeneic transplants can be used.

Pterygium

The results showed that CLAU significantly reduced the risk of pterygium recurrence compared to conjunctival transplants. Conjunctival-limbal autologous transplants reduced the risk of pterygium recurrence for primary pterygium compared to Mitomycin C, but this comparison did not reach statistical significance. Amniotic membrane transplantation and CLAU had similar low rates of recurrence (2 recurrences in 43 patients and 4 in 46, respectively), and the relative risk was not significant. Long-term complications were rare following CLAU, which indicates that the LSCT as an adjuvant to excision is a relatively safe procedure to reduce the risk of pterygium recurrence.

Therefore, there is moderate quality evidence that CLAU transplantations significantly reduced the risk of pterygium recurrence compared with conjunctival transplantation. The complication rates indicate that CLAU is a safe treatment option to prevent the recurrence of pterygium. However, the benefit of LSCT in Ontario is uncertain because the severity and recurrence of pterygium is unknown in Ontario.

Potential costs of offering LSCT for the treatment of non-ptyerygium LSCD in Ontario were examined. Assuming that LSCT is technically similar to corneal transplants, and that approximately 20 to 50 patients per year would benefit, the estimated average total cost per patient for performing a LSCT in Ontario is \$2,291.48 (Cdn) including hospital and physician fees (range, \$951.48 – \$4,538.48). Since 1999, 8 patients have received out of country LSCTs. The average cost of out of country LSCTs per eye was

Limbal Stem Cell Transplantation

\$18,735.20 (range, \$8,219.54 – \$33,933.32), and the average cost per patient was \$57,583 (range, \$8,219.54 – \$130,628.20).

Based on the above findings, OHTAC recommends the following with regard to LSCT:

OHTAC Recommendations

A) LSCT for the treatment of non-ptyerygium LSCD

While the evidence to support LSCT is weak, it is unlikely that, given the rarity of the condition, more robust evidence will be available. Therefore, OHTAC recommends that access to this technology be provided in a way that ensures alignment with the best available evidence as set out in the Medical Advisory Secretariat's analysis:

- Autologous LSCT is the treatment option of choice;
- If autologous LSCT is not possible, either living-related or cadaveric allogeneic LSCTs can be used; and
- Liberal use of amniotic membrane transplantations is questioned and should only be used for patients with severe LSCD.

Given the uncertainty regarding this technology, patient outcomes should be tracked.

B) LSCT as an adjuvant therapy to excision for the treatment of pterygium

The rate of pterygium recurrence after surgical excision and current standard adjuvant therapy is uncertain in Ontario. Recommendations regarding limbal stem cell transplantation as an adjuvant therapy to excision cannot be made until the recurrence rate is known. Thus, OHTAC recommends that the pterygium excision fee code be modified to include the identification of left or right eye so recurrence rates can be tracked.