OHTAC Recommendation

Extracorporeal Photopheresis

March 28, 2006

OHTAC Ontario Health Technology Advisory Committee

Extracorporeal Photopheresis

The Ontario Health Technology Advisory Committee (OHTAC) met on March 28 2006 to review the effectiveness, safety and cost-effectiveness of extracorporeal photopheresis (ECP) for the treatment of refractory erythrodermic cutaneous T-cell lymphoma (CTCL) and refractory chronic graft-verus-host disease (cGvHD).

Cutaneous T-Cell Lymphoma

CTCL is a general name for a relatively uncommon group of skin affecting disorders caused by malignant white blood cells (T lymphocytes). The most frequently diagnosed form of CTCL is mycosis fungoides (MF) and its leukemic variant Sezary syndrome (SS).

MF is an indolent lymphoma with patients often having several years of eczematous or dermatitic skin lesions before the diagnosis is finally established. MF is not life threatening. Most patients experience skin symptoms without serious complications.

A life-threatening syndrome in CTCL patients involves erythroderma (intense and usually widespread reddening of the skin, often preceding or associated with exfoliation) and circulating tumour cells. This is known as Sezary's Syndrome (SS). It has been estimated that approximately 5-10% of CTCL patients have SS.

Therapy for MF is topical chemotherapy, phototherapy, radiotherapy or total skin electron beam radiation (TSEB). Treatment of advanced erythrodermic disease (SS) usually consists of topical and systemic therapy. ECP is a potential option for patients with SS who are refractory to other forms of treatment.

Chronic Graft-Versus-Host Disease

Hematopoietic cell transplantation (HCT) is a treatment used for a variety of malignant and nonmalignant diseases of the bone marrow and immune system. The procedure is often associated with serious immunological complications, particularly GvHD. A chronic form of GvHD (cGvHD) afflicts many HCT recipients which results in dysfunction of numerous organ systems or even a profound state of immunodeficiency. The syndrome typically develops several months after transplantation.

Patients who develop cGvHD require reinstitution of corticosteroids and immunosuppressive medication (if already discontinued) or an increase in dosage and possibly addition of other agents. ECP is a salvage therapy that has been considered in patients with refractory cGvHD.

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The Technique

ECP is an immunomodulatory technique based on pheresis of light sensitive cells. Whole blood is removed from the patient and the lymphocytes are treated with methoxsalen (a drug that sensitizes malignant cells to ultraviolet A light [UVA]), exposed to UVA and then returned to the patient. Red blood cells and plasma are returned to the patient between each cycle.

Regulatory Issues

The UVAR XTS Photopheresis System® is licensed by Health Canada for the "palliative treatment of skin manifestations of CTCL." The device is not licensed for the treatment of cGvHD.

UVADEX® (methoxsalen) is not licensed by Health Canada for either indication, but has been used in Canada via the Special Access Program.

Status in Ontario

- Ontario residents who want ECP may be referred by physicians to an out of country (OOC) facility or a facility in Canada.
- Regulations require the OOC treatment to be medically necessary. It is not required that the patient be treatment resistant to other forms of therapy in order to consider ECP to be medically necessary.
- In 2004/05 MOHLTC approved 8 applications for 7 distinct patients for OOC ECP. The average amount paid per patient was $US 136,061.
- In 2005 1 Ontario patient began ECP in Alberta. The approved cost was $CDN 51,808.
- Two expert consultants jointly estimated that, as an upper estimate, there may be approximately 30 new treatment resistant erythrodermic CTCL patients and 30 new treatment resistant cGvHD patients per year in Ontario who are unresponsive to other forms of therapy and may be candidates for ECP.

Systematic Review of ECP

The Medical Advisory Secretariat (MAS) conducted a systematic review of the literature on the effectiveness of using ECP for the treatment of refractory erythrodermic CTCL and refractory cGvHD.

Based on the MAS analysis and following discussion, OHTAC found the following:

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1. *CTCL*

Overall, there is low quality evidence that ECP improves response rates and survival in patients with erythrodermic CTCL who are unresponsive to other forms of therapy. Limitations in the literature related to ECP for the treatment of refractory erythrodermic CTCL include the following:

- Heterogeneity in treatment regimens and diagnostic criteria.
- Most studies are uncontrolled, retrospective case series.
- Small sample sizes.
- Response criteria not clearly defined or inconsistent (e.g., the definition of a complete response in the studies varied from greater than 75% improvement to complete clearance [100%] of skin lesions).
- Unclear how concomitant therapy (both systemic and topical) also contributed to patient responses.

2. *cGvHD*

Overall, there is low quality evidence that ECP improves response rates and survival in patients with cGvHD who are unresponsive to other forms of therapy. Limitations in the literature related to ECP for the treatment of refractory cGvHD were similar to those for refractory erythrodermic CTCL.

3. *Considerations*

- Key opinion leaders in the field agree that a field evaluation is feasible.
- Since methoxsalen is not approved by Health Canada, a field evaluation would be in compliance with Health Canada's Clinical Trial Application regulation.

OHTAC Recommendations

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

- ECP be conditionally funded for the treatment of refractory erythrodermic CTCL and refractory cGvHD in the context of a 2 year field evaluation.

- Patient inclusion criteria must be developed by experts in the field (standardized definitions to measure disease outcomes including response rates, quality of life, morbidity).

- Final recommendations to be made by OHTAC based on the results from the 2 year field evaluation and also predicated on the Health Canada regulatory status for methoxsalen and the photopheresis system