1. Introduction

Extra-corporeal photopheresis has a significant body of clinical evidence to support its use in the treatment of steroid refractory chronic graft versus host disease (cGvHD) and cutaneous T-cell lymphoma (CTCL). The majority of the evidence available is derived from observational studies rather than randomised controlled trials. However, the findings of the clinical studies are consistent for the main part and it is accepted that randomised controlled trials in these indications are difficult to establish. As such, reviews of the clinical evidence have come to the conclusion that ECP has a role to play in the management of both CTCL and chronic GvHD (McKenna et al. 2006; Norcom 2005).

To date, there have been no published economic evaluations of ECP in either of these indications. This paper attempts to develop a simple economic analysis of ECP based on the available clinical evidence. The findings are intended to provide an indication of the cost effectiveness of ECP.

2. Methods

2.1 Development of the analysis

A simple economic model was developed in Microsoft Excel to compare the costs and outcomes of ECP with the standard of care in CTCL and cGvHD. The model synthesises data on survival, quality of life and treatment costs from a number of sources. The findings of the model are expressed in terms of cost per quality adjusted life year (QALY).

2.2 Data and Sources

2.2.1 Effectiveness of ECP in CTCL

Treatment effectiveness for the purposes of the analysis was defined in terms of survival. According to the British Association of Dermatology (BAD) guidelines, the mean survival for CTCL patients with sezary syndrome (SS) was 39 months under standard treatments (Whittaker et al. 2003). This was used in the base case analysis of CTCL. The mean survival for confirmed erythrodermic CTCL of 30 months under standard treatment was used in sensitivity analysis (Lamberg et al. 1984).

A number of studies report the survival of CTCL patients treated with ECP, with median survival ranging from 30 months (Kim et al. 1995) to over 100 months (Gottlieb et al 1996). A number of other studies have reported survival within this range, including 60 months (Heald et al. 1992), 70 months (Jiang et al 1999) and 96 months (Zic et al. 1996).
The comparability of these findings is hindered by heterogeneity in the study populations (e.g. not all patients had proven erythrodermic disease) and small sample sizes.

For the purposes of this analysis, we assumed a median survival of 60 months for CTCL patients treated with ECP. Sensitivity analysis using the lower (30 months) and upper estimates (100 months) reported in the literature was also considered.

**Quality of life data**

Quality of life data was derived from published sources. Utility scores for CTCL patients treated with ECP were derived from a 9-year retrospective study at a single institution that assessed 29 patients with CTCL who were actively being treated with 1 month or more of ECP alone or with adjuvant therapy (Bisaccia et al. 2000). The mean utility score was 0.68 for patients with T3/T4 CTCL disease, 0.8 for patients with T2 disease, and 0.96 for patients that achieved remission. The mean quality of life score with T3/T4 was applied in this analysis. The mean quality of life score with remission was used in sensitivity analysis.

Utility under standard treatment was an assumption based on the preference score (0.5) for combined modality therapy in early stage Hodgkin’s disease for 8.4 months (Source: Preference Weights 1998-2001). The preference score (0.7) for chemotherapy in early stage Hodgkin’s disease for 6 months was used in sensitivity analysis (Source: Preference Weights 1998-2001).

A summary of the outcomes data used in the CTCL analysis is presented in the table below.

**Table 1:** Effectiveness data and sources for the model on ECP for CTCL

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Survival (Months)</th>
<th>Sources</th>
<th>Utility</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECP</td>
<td>60&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Heald et al. 1992</td>
<td>0.68</td>
<td>Bisaccia et al. 2000</td>
</tr>
<tr>
<td>Standard treatment</td>
<td>39&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Whittaker et al. 2003</td>
<td>0.50</td>
<td>Preference Weights 1998-2001</td>
</tr>
</tbody>
</table>

Note: 1. median survival; 2. mean survival.

**Costs**

The treatment costs of ECP and standard care were derived from an unpublished analysis developed for the National Specialist Commissioning Advisory Group (NSCAG) (Table 2). The cost for standard treatment was a weighted average cost of single agent chemotherapy and combination chemotherapy. Treatment costs over a 3 year period were estimated. Future costs were discounted at an annual rate of 3.5%, as recommended by NICE (2004). The impacts of an annual discount rate of 0% and 6% for costs were examined in sensitivity analysis.
Table 2: Annual treatment costs per patient for CTCL

<table>
<thead>
<tr>
<th>Year</th>
<th>ECP</th>
<th>Current Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>£24,573</td>
<td>£34,425</td>
</tr>
<tr>
<td>Year 2</td>
<td>£10,839</td>
<td>£43,357</td>
</tr>
<tr>
<td>Year 3</td>
<td>£5,420</td>
<td>£21,679</td>
</tr>
<tr>
<td>Total</td>
<td>£40,832</td>
<td>£99,461</td>
</tr>
</tbody>
</table>

2.2.2 Effectiveness of ECP in cGvHD

Survival rates for standard care and ECP in the treatment of cGvHD were derived from published sources. Survival data for standard treatment were based on the results of the most widely employed first line therapy for treatment of chronic GVHD, a ciclosporin A (CSA) and prednisone regime (Higman et al. 2004). Sullivan et al. (1988a) reported that in high-risk patients, treatment with prednisone alone resulted in only 26% 5-year survival. When a similar group of patients was treated with alternating day CSA and prednisone, the 5-year survival exceeded 50% (Sullivan et al. 1988b).

Given that the analysis was considering a 3 year period, a survival rate of 50% at 3 years was assumed for the standard care arm.

The baseline survival data for ECP were derived from two studies. Miller at al. (2004) conducted a retrospective study of 55 patients at high risk or ineligible for a conventional allogeneic hematopoietic stem cell transplant who received a regimen consisting of ECP, pentostatin, and reduced dose total body irradiation. After the median follow-up of 502 days, the 1-year, 2-year and overall survival rates were 67%, 58%, 55% respectively. Greinix et al. (2000) reported survival rate of 53% at 4 years for patients treated with ECP after stem cell transplantation. The higher 15-month and 5-year survival rates reported by Greinix (1998) and Messina et al. (2003) and the lower 1-year and 5-year survival rates reported by Daniel et al (2006) were examined in sensitivity analysis.

Quality of life data

Utility data were also derived from published literature. In a retrospective study of 44 children with chronic GVHD, Messina et al. (2003) reported that after treatment with ECP, the patients’ quality of life, measured as the median Lansky/Karnofsky score, improved from 60% (range 30-90%) at the start of ECP to 90% (range 60–100%). According to the revised Seattle classification, the Karnofsky or Lansky Clinical Performance scores for clinical extensive chronic GVHD was less than 60% (Lee et al. 2003). This was used in the model for the standard treatment for cGVHD. The preference score (0.9) for the standard treatment arm in sensitivity analysis was also derived from published sources (Source: Preference Weights 1998-2001).

Table 3 presents a summary of the outcomes data used in the analysis of cGvHD.
Table 3: Outcomes data and sources for model on ECP for cGVHD

<table>
<thead>
<tr>
<th>Effectiveness</th>
<th>ECP Value</th>
<th>Source</th>
<th>Standard treatment Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of survival</td>
<td>Year 1 0.67</td>
<td>Miller et al. 2004</td>
<td>Year 1 0.65</td>
<td>Assumption</td>
</tr>
<tr>
<td></td>
<td>Year 2 0.58</td>
<td>Miller et al. 2004</td>
<td>Year 2 0.55</td>
<td>Assumption</td>
</tr>
<tr>
<td></td>
<td>Year 3 0.55</td>
<td>Assumption based on 4- and 5-year survival by Greinix et al. 2000 and Miller et al. 2004</td>
<td>Year 3 0.50</td>
<td>Assumption based on 5-year survival by Sullivan et al. 1988b</td>
</tr>
<tr>
<td>Utility</td>
<td>0.9</td>
<td>Messina et al. 2003</td>
<td>0.6</td>
<td>Lee et al. 2003</td>
</tr>
</tbody>
</table>

Costs
The treatment costs of ECP and standard care were derived from an unpublished analysis developed for the National Specialist Commissioning Advisory Group (NSCAG) (Table 4). The cost of ECP included the cost of ECP drug and capital, ECP clinic cost, hotel and travel cost, supportive care cost and steroid cost. The cost of treating patients with standard treatment included the cost of steroids plus CSA, clinic costs and cost of supportive care.

Treatment costs over a 3 year period were estimated. Future costs were discounted at an annual rate of 3.5%, as recommended by NICE (2004). The impacts of an annual discount rate of 0% and 6% for costs were examined in sensitivity analysis.

Table 4: Treatment costs per patient for cGVHD

<table>
<thead>
<tr>
<th>Cost per patient (£)</th>
<th>ECP</th>
<th>Standard treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>£37,523</td>
<td>£13,062</td>
</tr>
<tr>
<td>Year 2</td>
<td>£8,850</td>
<td>£16,574</td>
</tr>
<tr>
<td>Year 3</td>
<td>£4,233</td>
<td>£6,144</td>
</tr>
<tr>
<td>Cost of treating infection (3 years)</td>
<td>£7,125</td>
<td>£10,688</td>
</tr>
<tr>
<td>Total cost</td>
<td>£57,731</td>
<td>£46,468</td>
</tr>
</tbody>
</table>

3. Results
The costs and outcomes data presented above were combined to produce a simple cost effectiveness analysis of ECP compared to standard treatment in both CTCL and cGvHD. The findings are summarised below.
3.1 CTCL

Table 5: Results on ECP for CTCL

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total cost(^1) (£)</th>
<th>Incremental Cost(^2) (£)</th>
<th>Total QALY</th>
<th>Incremental QALY(^2)</th>
<th>ICER(^1,2) (£/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECP</td>
<td>39,580</td>
<td>-54,873</td>
<td>3.4</td>
<td>1.78</td>
<td>-30,914</td>
</tr>
<tr>
<td>Standard treatment</td>
<td>94,452</td>
<td>1.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: 1: Future costs were discounted at an annual rate of 3.5%.
2: ECP over standard treatment.

For a patient with erythrodermic CTCL, the total treatment cost with ECP for 3 years was £39,580, compared to £94,450 with standard treatment in the same period. The incremental cost of ECP compared to standard treatment was -£54,873 (i.e. ECP is less costly than standard treatment over 3 years).

Combining the survival data with the utility data, it was possible to derive an estimate of the quality adjusted life years (QALYs) resulting from each treatment arm. The total QALY gained was 3.40 under ECP and 1.63 under standard treatment, resulting in an incremental QALY of 1.78.

Combining the costs and benefit produced an incremental cost utility ratio of -£30,914 per QALY. The negative ICER indicates that ECP dominates the standard treatment for ECP, i.e. ECP is more effective and less costly than the standard treatment.

Sensitivity analyses showed that the above results were insensitive to a wide range of alternative values for the costs of treatment, survival and utility.

3.2 cGVHD

Table 6: Results on ECP for cGVHD

<table>
<thead>
<tr>
<th></th>
<th>ECP</th>
<th>Standard treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cost(^1) (£)</td>
<td>56,728</td>
<td>44,764</td>
</tr>
<tr>
<td>Incremental cost(^2) (£)</td>
<td>11,964</td>
<td></td>
</tr>
<tr>
<td>Total QALY(^1)</td>
<td>1.54</td>
<td>0.97</td>
</tr>
<tr>
<td>Incremental QALY(^2)</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>ICER(^1,2) (£/QALY)</td>
<td>21,059</td>
<td></td>
</tr>
</tbody>
</table>

Notes: 1. Both future costs and benefits were discounted at an annual rate of 3.5%.
2. ECP over standard treatment.

The total cost of treating a patient with cGVHD over three years was £56,728 using ECP and £44,764 using standard treatment. The incremental cost was £11,964.

The total QALYs gained over three years was 1.54 with ECP compared to 0.97 with standard treatment. ECP therapy resulted in 0.57 QALYs more than standard treatment.
The incremental cost utility ratio of ECP over standard treatment for cGVHD was £21,059 per QALY.

The above results were insensitive to the discount rates, survival under standard treatment and the costs of treating infections associated with ECP or standard treatment. The results were most sensitive to the utility under standard treatment and under ECP, the survival rates of ECP and the cost of ECP treatment in year 1.

4. Discussion
There is a reasonable body of clinical evidence to support the use of ECP in the management of CTCL and cGVHD. Limitations in the literature related to ECP for the treatment of both refractory erythrodermic CTCL and cGVHD 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.
- Unclear how concomitant therapy (both systemic and topical) also contributed to patient responses.
- Quality of life reported in only a very few case series.

However, the body of evidence is sufficient to support the inclusion of ECP in treatment guidelines (Norcom 2005; National Cancer Institute). This analysis attempted to provide an estimate of the cost effectiveness of ECP in the treatment of CTCL and cGVHD compared to standard care.

Conservative estimates on effectiveness were applied in the analysis of CTCL. Despite this, the findings still suggest that ECP is more effective and less costly than standard treatment for CTCL. The results were insensitive to a wide range of alternative values for key variables used in the sensitivity analysis.

Similarly, based on conservative assumptions on survival data for ECP, we found that ECP was more expensive than standard treatment for cGVHD but it was also more effective with an incremental cost effectiveness ratio of £21,059 per QALY. This is well within the accepted threshold of £30,000 per QALY that is usually used by NICE. However, these results were sensitive to variation in the utility scores applied, the survival rates of ECP and the cost of ECP in year 1. If ECP is to be used on a more widespread basis in the treatment of cGvHD then this should be accompanied by ongoing data collection to confirm these findings.
References


