COST-EFFECTIVENESS OF EXTRACORPOREAL PHOTOPHERESIS FOR THE TREATMENT OF ERYTHRODERMIC (STAGE T_4, M_0) CUTANEOUS T-CELL LYMPHOMA PATIENTS IN THE AUSTRALIAN SETTING

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BACKGROUND AND OBJECTIVE

- Cutaneous T-cell lymphoma (CTCL) is a rare and incurable form of non-Hodgkin's lymphoma that causes debilitating pruritus, skin lesions and plaques that significantly impact quality of life. It is estimated there are less than 1,200 CTCL patients in Australia.[1]
- The objective of this study was to assess the cost-effectiveness of extracorporeal photopheresis (ECP) compared with standard of care (SoC) therapy for the treatment of erythrodermic (stage T_4, M_0) CTCL patients, who are refractory to one or more systemic treatments from the perspective of the Australian health care system.

METHODS

Population

- Patients with erythrodermic Stage T_4, M_0 CTCL aged 18 years and older who are refractory to one or more systemic treatments.

Intervention and comparators

- A survey and assessment of published literature was conducted to determine the placement of ECP and the comparator therapies.
- Comparator was Standard of Care second-line therapies including methotrexate (MTX), interferon-alpha (IFN-α), vorinostat, and brentuximab vedotin (BV).

Model Structure

- Cost-effectiveness of ECP compared with other SoC therapies available in Australia (e.g. MTX, IFN-α vorinostat and BV).
- Patients with CTCL often cycle through multiple second-line therapies as well as chemotherapy.[2] Therefore, patients were modelled to cycle through different 2nd line therapies before chemotherapy or no treatment.
- The model assumes that following discontinuation of initial treatment, patients follow a fixed sequence of treatments determined by cost of treatment (i.e. cheapest to most expensive) (Figure 1).
  - Patients received chemotherapy once all other treatment options were exhausted, after which it is assumed patients no longer received active therapy.
- Treatment sequence and model structure was validated using a Markov trace of the ECP arm (Figure 2).
- Monthly treatment regimens for therapy were calculated using relevant treatment guidelines and product information sheets.[3,4]
- Patients were assigned costs (in A$) and quality-adjusted life years (QALYs) associated with each treatment at monthly cycle intervals over a 5-year time horizon.
- Results were presented comparing ECP vs a weighted SoC comparator. Weighting of each comparator arm was calculated based on treatment survey and Services Australia prescribing data.

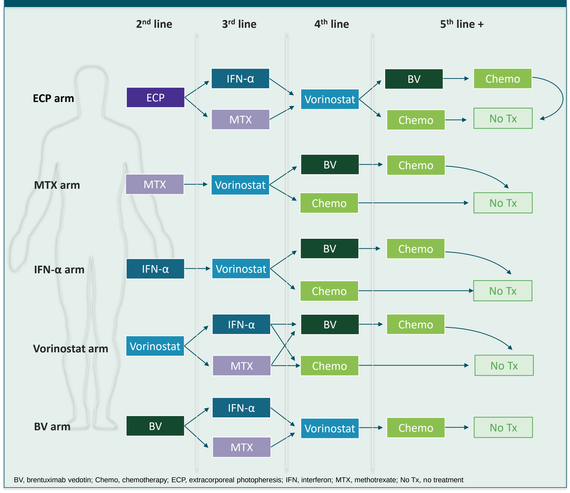
Transition Probabilities

- Time to next treatment (TTNT) used to calculate time in each health state for each therapy, was sourced from an Australian observational study of ECP and comparator treatments (Figure 3).[2]
  - The study had the highest external validity as the model is from the perspective of the Australian public payer.
  - Patients received ECP therapy at a median 2nd line of treatment.[2]
  - TTNT provides a functional and clinically relevant measure of therapy effectiveness, as it implies durability of response and control of debilitating symptoms.
  - In the absence of progression free survival data, TTNT data presented in Gao 2019 and associated unpublished data collected from the Victorian Comprehensive Cancer Centre (VCCC; Melbourne, VIC, AUS) was used to construct Kaplan-Meier (KM) curves.[2]
  - The IFN-α TTNT KM curve was used as a proxy to calculate the probability of discontinuing BV given that a BV KM curve source was unavailable and the mean time on treatment in the BV clinical trial [5] was similar to the median TTNT for IFN-α (8.9 months versus 8 months, respectively).[2]
- Baseline mortality was based on the overall survival (OS) analysis for ECP presented in Gao 2019 and the VCCC report.[2]
  - Conservatively, no survival benefit was assigned to the ECP arm and mortality reported for ECP applied to all treatment arms. Median OS was 80 months.

Costs

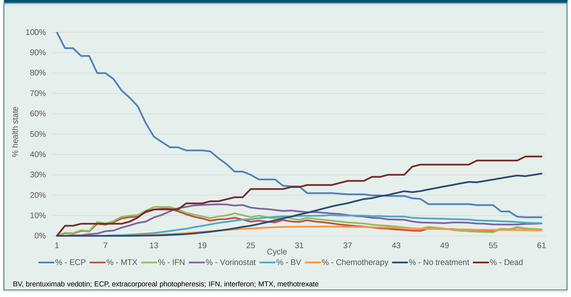
- Only treatment costs were considered in this economic analysis.
- The cost of ECP included the cost of the ECP procedure plus the cost of extracorporeal methoxsalen, UVADEX® (Mallinckrodt Pharmaceuticals plc, Bedminster, NJ, USA).
- The ECP treatment protocol applied in the model is based on international guidelines [6]:Two consecutive days of treatment per month for six months, then one treatment every six weeks thereafter.
  - The ECP regimen used in Australia differs slightly from international guidelines primarily due to complex funding arrangements in individual hospitals and lack of resources.[7]
  - The Australian regimen has been shown to produce similar outcomes as the international protocol [7] and the average cost per month is similar.
- Drug costs were sourced from the PBS, and cost per cycle calculated using the respective treatment regimens as indicated in product information sheets and international guidelines.
- Other costs such as treatment-related adverse event (AE) costs were conservatively not included in the model, given the number of Grade 3 or 4 AEs associated with comparator therapies.[5, 8-11]

Figure 1. Structure of the economic evaluation



BV, brentuximab vedotin; Chemo, chemotherapy; ECP, extracorporeal photopheresis; IFN, interferon; MTX, methotrexate; No Tx, no treatment

Figure 2. Markov trace of the ECP arm



BV, brentuximab vedotin; ECP, extracorporeal photopheresis; IFN, interferon; MTX, methotrexate

Figure 3. Inputs used in the economic analysis

Variable description	Value	Source
Median TTNT (Months)		
ECP	14	[2][b]
Methotrexate	2.5	
IFN-α	8	
Vorinostat	7.5	
BV	8[a]	
Chemotherapy	3	
Cost per month (AU$)		
ECP	Month 1 to 5: $4,448.50 Month 6+: $1,611.92	PBS; expert opinion
Methotrexate	$13.67	PBS; [4]
IFN-α	$1,383.19	PBS; TGA PI
Vorinostat	$4,519.20	PBS; TGA PI
Brentuximab	$21,779.57	PBS; [3]
Chemotherapy	$698.57	Assumption
No treatment	$0	PBS; expert opinion
Utility		
ECP	0.73	[7, 12]
Methotrexate	0.62	[5, 12]
IFN-α	0.70	[12, 14, 15]
Vorinostat	0.65	[12, 16]
BV	0.68	[12, 17]
Chemotherapy	0.59	[12]
No treatment	0.59	[12]
Disutility		
ECP	NA	
Methotrexate	-0.040	[9]
IFN-α	-0.095	[9]
Vorinostat	-0.018	[8, 10]
BV	-0.058	[5, 11]
Chemotherapy	NA	
No treatment	NA	
Other		
Time horizon	5 years	
Discounting	5%	MSAC

BV, brentuximab vedotin; ECP, extracorporeal photopheresis; IFN, interferon; MSAC, Medical Services Advisory Committee; NA, not applicable; PBS, Pharmaceutical Benefits Scheme; TGA, Therapeutic Goods Administration; TTNT, time to next treatment [a] assumed same as IFN; [b] including unpublished data from the Gao 2019 study

Figure 4. Results of the economic analysis

Tx arm	Costs	Incr. cost	QALYs	Incr. QALYs	ICER
ECP	$145,514	NA	2.33	NA	NA
Weighted comparator	$183,106	-$37,591.99	2.13	0.20	Dominant

ECP, extracorporeal photopheresis; ICER, incremental cost-effectiveness ratio; Incr, incremental; NA, not applicable; QALY, quality adjusted life years

Figure 5. Results of deterministic sensitivity analyses

Description	Incr. cost	Incr. QALY	ICER	Impact
Base case	-$37,592	0.20	Dominant	NA
Discount rate 0%	-$38,512	0.22	Dominant	Low - Favours ECP
Discount rate 3.5%	-$37,893	0.21	Dominant	Low - Favours ECP
Gao 2019 ECP treatment regimen	-$31,642	0.20	Dominant	Low - Favours comparator
No disutility associated with treatment	-$37,592	0.17	Dominant	Low - Favours comparator
Use vorinostat TTNT for BV	-$27,507	0.21	Dominant	Low - Favours comparator
Monthly cost of BV discounted by 50%	-$3,645	0.20	Dominant	Moderate - Favours comparator

BV, brentuximab vedotin; CTCL, cutaneous T-cell lymphoma; ECP, extracorporeal photopheresis; ICER, incremental cost-effectiveness ratio; Incr, incremental; TTNT, time to next treatment, QALY, quality adjusted life years

METHODS

Utilities

- A systematic review of the literature did not identify any relevant publications of utility values associated with CTCL.
  - A clinician survey identified psoriasis as the most applicable disease to use as a proxy for QOL as patients with psoriasis suffer from pruritis, have physical disfigurement and erythroderma; all of which are symptoms suffered by CTCL patients.[7]
  - One psoriasis QOL study [12] was the most appropriate as it had been applied in previous health technology assessments in Australia and the UK.[13]
  - Psoriasis severity was mapped to CTCL treatment response; mild, moderate and severe psoriasis mapped to complete, partial and no response, respectively.
- Weighted utility values for each treatment were calculated based on responder rates reported in the clinical evidence.[5, 7, 12, 14-17] It was assumed that no response was achieved with chemotherapy.
- All comparator therapies are associated with Grade 3 and 4 AEs, and therefore disutilities were applied and calculated based on frequency and severity using clinical evidence and existing publications.[5, 8-11]
- Given that no Grade 3 or 4 AEs were attributed to ECP treatment in the Gao study, there was no disutility applied to the ECP arm.[2]
- No disutility was applied to the chemotherapy arm under the assumption of no response to treatment.

Sensitivity analysis

- Deterministic sensitivity analysis was conducted to assess the impact of various assumptions and other plausible scenarios on the projected outcome. The following assumptions and scenarios were tested:
  - Discounting at 0% and 3%
  - Australian approved ECP treatment regimen
  - Disutilities were removed
  - Vorinostat TTNT was applied to the BV arm.
  - The price of BV examined given its confidential effective price under the PBS.

RESULTS

- Including ECP as a second-line treatment option for CTCL dominated over other treatment strategies in terms of cost-effectiveness (Figure 4).
- ECP displaced expensive pharmaceutical therapies (i.e. a greater proportion of patients avoided subsequent treatment with the high-cost treatment options vorinostat and brentuximab vedotin).
- ECP was associated with an incremental quality-adjusted life year (QALY) gain of between 0.20 and 0.21, due to the lack of Grade 3 or 4 AEs and because patients remained on therapy for longer with a higher quality of life than comparator treatments.
- ECP is the dominant treatment option in all sensitivity analysis scenarios (Figure 5).
  - Discounting monthly cost of BV by 50% had the greatest impact on the ICER, however, ECP remained dominant over the weighted comparator.

CONCLUSION

- This analysis demonstrates that ECP is a cost-effective option for the treatment of erythrodermic CTCL patients, who are refractory to one or more systemic treatments, in Australia, compared with other SoC therapies.
- ECP displaced expensive pharmaceutical therapies and delayed advancing to high-cost treatment alternatives vorinostat and brentuximab vedotin, which lead to ECP being both less costly and more effective.

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