DOI 10.1111/j.1365-2133.2006.07483.x

Economic evaluation of methyl aminolaevulinate-based photodynamic therapy in the management of actinic keratosis and basal cell carcinoma

K. Caekelbergh,* L. Annemans,*† J. Lambert‡ and R. Roelandts§

*HEDM (Health Economics and Disease Management), Brussels, Belgium
†Faculty of Medicine, University of Ghent, Ghent, Belgium
‡Department of Dermatology, University Hospital Antwerp, Antwerp, Belgium
§Photodermatology Unit, University Hospital Leuven, Leuven, Belgium

Correspondence
Lieven Annemans.
E-mail: lannemans@be.imshealth.com

Accepted for publication
18 May 2006

Key words
actinic keratosis, basal cell carcinoma, cost, Delphi panel, methyl aminolaevulinate-based photodynamic therapy

Conflicts of interest
None declared.

Summary

Background Various effective therapeutic options are currently available for the treatment of actinic keratosis (AK) and basal cell carcinoma (BCC), but none is perfect. Poor cosmesis resulting from surgical procedures and skin irritation induced by topical agents remain significant problems.

Objectives To evaluate the cost-effectiveness of a recent approach, methyl aminolaevulinate-based photodynamic therapy (MAL-PDT; Metvix®; Galderma, Lausanne, Switzerland) in AK and BCC.

Methods A medical decision tree was developed for simulation of all possible outcomes associated with the medical decision to apply MAL-PDT or a comparator. The time horizon was 1 year for AK and 5 years for BCC. The comparators were cryotherapy in AK and excision surgery in BCC. Clinical data for the model were obtained from the literature. Data on medical management resulted from a Delphi panel performed among 12 Belgian dermatologists. Based on the model, the cost per full responder was calculated, whereby a responder was defined as a patient with all lesions clinically responding and showing an excellent cosmetic result.

Results MAL-PDT is a more expensive treatment compared with cryotherapy for AK. However, the cost per full responder is comparable with cryotherapy (€363 and €379, respectively). Incremental cost per extra full responder is €401. Incremental cost per full responder is €469 for nodular BCC and €251 for superficial BCC, both compared with excision surgery.

Conclusions The results suggest that MAL-PDT is a cost-effective intervention in AK taking a 1-year time horizon, if society is willing to pay €1·50 per day of response, and that MAL-PDT is better value for money than excision in BCC, taking a 5-year time horizon.

Actinic keratoses (AKs) or solar keratoses are common dysplastic epidermal lesions which occur in pale-skinned individuals who are chronically exposed to sunlight. It has been estimated that up to 60% of predisposed persons older than 40 years of age have at least one AK.[1,2] AKs are considered to be precancerous lesions and it is shown that AK is the most important predisposing factor for squamous cell carcinoma.[3] Frost and Green[4] reported that prevalence rates of AK range from 11% to 25% in various northern hemisphere populations. In comparison, among Australian adults the range is from 40% to 60%.[4] In Belgium, 49 000 diagnoses of AK per year are reported (IMS database, 2003; unpublished data).

Basal cell carcinoma (BCC), a slow-growing, locally malignant epidermal skin tumour, is the most frequent cutaneous cancer among white people, and represents 75% of all nonmelanoma skin cancers (NMSC).[5] Figures from the Belgian Cancer Register[6] indicated an incidence of NMSC of 7·1 per 100 000 in women (1997) and 8·9 per 100 000 in men. BCC is excluded from these figures. If we assume that 75% of all NMSC are BCC,[5] an incidence of 26·7 per 100 000 in men is

applicable in Belgium ($3 \times 8{\cdot}9$), and 21·3 per 100 000 ($3 \times 7{\cdot}1$) in women.

Various effective therapeutic options are currently available for the treatment of AK and BCC, e.g. topical treatments, cryotherapy, curettage, excision and radiotherapy, but none is perfect. For instance, poor cosmesis resulting from surgical procedures and skin irritation induced by topical agents remain significant problems.

Methyl 5-aminolaevulinate (MAL; Metvix®; Galderma, Lausanne, Switzerland) is a 160 mg g^{-1} cream (2 g per tube) which, in combination with red light, is applied in the treatment of AK and BCC. MAL-based photodynamic therapy (PDT) has been studied in randomized clinical trials and has shown good lesion responses compared with cryotherapy and placebo in AK.[7] In BCC, MAL-PDT is as effective in terms of clinical response rate at 3 months as excision surgery (91% vs. 98%, respectively), which is the most common option today in this indication.[8] With excision surgery, however, more patients show a poor cosmetic outcome compared with MAL-PDT.

In healthcare decision making, not only clinical results but also economic arguments need to be considered. Indeed, in the current healthcare environment, the budgets are limited, and healthcare interventions are no longer evaluated on efficacy and safety alone. The cost-effectiveness (value for money) is becoming an increasingly important criterion to assess new medical technologies that are submitted for reimbursement. Cost-effectiveness analysis implies firstly that the net costs of one intervention (B) vs. another (A) are considered, whereby net cost = (cost of intervention B − A) − (savings with B − A).

In a second step, the net costs are then balanced with the net effects of B vs. A. The ratio between the net costs and the net effects is called the incremental cost-effectiveness ratio. If this ratio is low, according to societal standards or according to existing benchmarks, the investment B is said to be cost-effective, i.e. to provide value for money.

In this paper, we describe the methods and results of a cost-effectiveness analysis of MAL-PDT in AK and BCC, whereby effects are expressed as patients having full response and number of days with response, and whereby response is defined as full clinical response and excellent cosmetic outcome.

Materials and methods

A medical decision tree was developed in order to simulate all possible outcomes associated with the medical decision to use MAL-PDT or a comparator. A time horizon for the simulation of 1 year was considered to cover the relevant costs and outcomes of management of AK, while a 5-year horizon was chosen for BCC. A discount rate of 3% per annum was applied from year 2 on. The time horizon of 1 year in AK was chosen to take into account the outcomes of second-line treatment. Ideally, a longer time horizon should be applied, in order to take into account recurrences beyond 1 year, but we did not find such data. In BCC, however, different studies report on recurrence rates up to 5 years, hence here this time horizon was applied. The comparator in AK was cryotherapy, while the comparator in BCC was excision surgery. These were chosen because they are common current alternatives in the respective indications, and both have been compared with MAL-PDT in prospective randomized trials.[7,8]

Radiotherapy was not chosen as comparator to MAL-PDT for the treatment of BCC because the position of radiotherapy/X-ray therapy in the treatment of BCC has been questioned. Radiotherapy/X-ray therapy is no longer frequently used in Belgium for treatment of BCC, mainly because the long-term cosmetic outcome is less than with other treatment modalities. The cosmetic outcome is important because most BCCs are on exposed, and thus visible, sites. Another drawback is that relapses later on are more difficult to treat in areas that have already been irradiated. An additional practical problem is the lack of experience of many dermatologists and the expensive equipment needed to perform radiotherapy. The patient can, of course, be transferred to a radiologist, but this makes the treatment procedure and the follow up more complicated.

The analytical perspective was that of the Belgian public health insurance Rijksinstituut voor Ziekte- en Invaliditeitsverzekering/Institut National d'Assurance Maladie (RIZIV/INAMI). Only direct medical costs were considered. The target population consisted of a cohort of patients with AK and BCC. More specifically, the study target population included: (i) in the AK analysis: patients with AK lesions > 5 mm in diameter on the face or scalp; and (ii) in the BCC analysis: (a) patients with primary nodular BCC (nBCC) lesions suitable for simple excision surgery and (b) patients with superficial BCC (sBCC) lesions suitable for cryosurgery. This means nBCC and sBCC in the H-zone (around the eyes or near the nasolabial or retroauricular folds), or patients with a large sBCC or nBCC lesion not in the H-zone.

Model description

The model was constructed in Excel 2000 and reflects the evolution of patients treated with MAL-PDT or with other modalities. The model reflects the probabilities of nonresponse, recurrence and adverse cosmetic outcomes for each alternative. Clinical data to populate the model were obtained from published literature, in particular the phase III programme for MAL-PDT. To collect data on medical management and resource use in different scenarios a Delphi panel was conducted in a sample of 12 Belgian dermatologists. Moreover, in-depth interviews with two dermatologists and one cosmetic surgeon were undertaken in order to validate the model.

Based on the model, the cost per 'full responder' was calculated, whereby a full responder was defined as a patient with clinically responding lesions *and* an excellent cosmetic result, defined as in the MAL-PDT clinical trial programme. The time horizon was 1 year for the model of AK, and 5 years for the model of BCC.

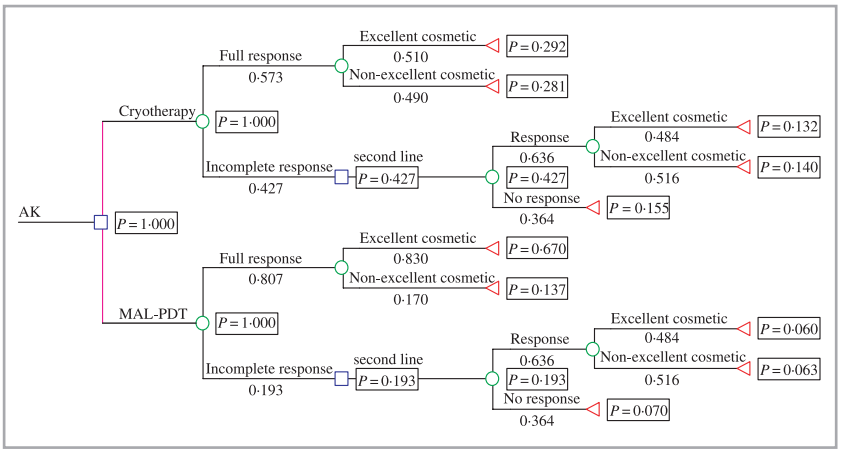

Fig 1. Medical decision tree for actinic keratosis (AK). The applied probabilities are explained in the text. MAL-PDT, methyl aminolaevulinate-based photodynamic therapy.

The model for AK is shown in Figure 1. The model consists of initial management (MAL-PDT or cryotherapy), second-line management and follow-up cosmetic assessment. After initial management, patients may have a full clinical response (meaning that 100% of the patient's lesions show a complete response, as assessed by the physician) or not. In the latter case, the remaining lesions receive second-line treatment. In patients in whom all lesions are cured, cosmetic outcome may be excellent or nonexcellent.

The type of second-line management after first-line failure on cryosurgery was obtained from the Delphi panel and thus reflects current practice. If the first line was MAL-PDT, the same second-line management as with current management was assumed. In the follow-up assessment, for patients with a nonexcellent cosmetic outcome, additional interventions were considered, such as reconstructive surgery or treatment of pigment anomalies with creams.

The total cost per year for a treatment is calculated as: cost of first-line treatment × 100% + cost of second-line treatment × percentage of patients showing incomplete response to first-line treatment + cost of follow-up management (excellent cosmetic outcome) × percentage of patients with excellent cosmetic outcome + cost of follow-up management (nonexcellent cosmetic outcome) × percentage of patients with nonexcellent cosmetic outcome. Full response is defined as healing of all lesions together with an excellent cosmetic outcome.

The model for BCC, where MAL-PDT was compared with excision surgery, was constructed in a similar way, with the exceptions that other second-line options are considered, that recurrence is possible, and that the time horizon is 5 years. Also, a distinction is made between nBCC and sBCC, given the different clinical outcomes. Although the model runs over 5 years in order to allow for recurrence, the response parameter was defined in the same way as for AK; this was done for the sake of comparison between the two conditions, with regard to the outcome parameter. It is a conservative approach, as the cosmetic outcomes should get better with time. Figure 2 shows the structure of the medical decision tree in BCC.

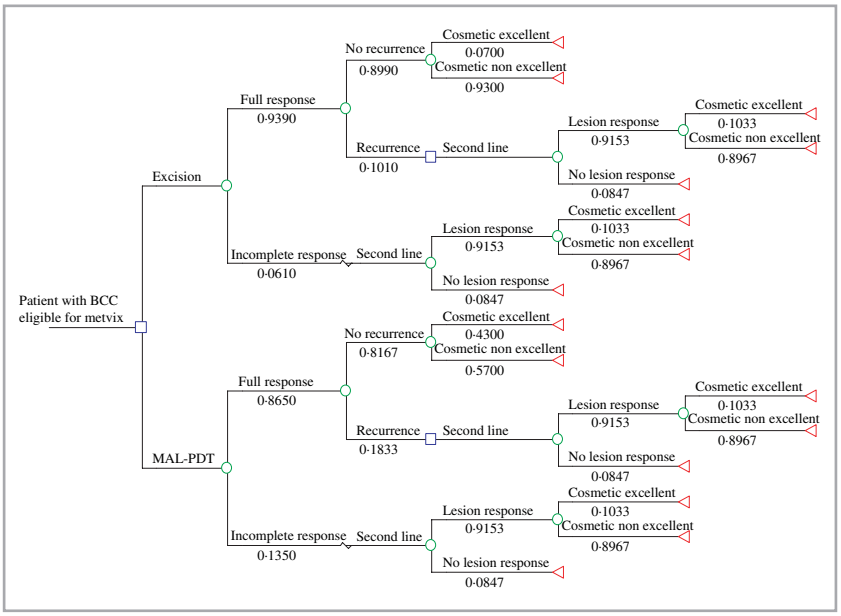

Fig 2. Medical decision tree for basal cell carcinoma (BCC) (example: nodular BCC). The applied probabilities are explained in the text. MAL-PDT, methyl aminolaevulinate-based photodynamic therapy.

Data input in the model

Clinical data input

Figures 1 and 2 show the probabilities applied in the medical decision tree for AK and nBCC. The clinical data for input in the model are derived from the phase III programme.

In AK, data are based on a large, multicentre phase III clinical study in which MAL-PDT was compared in a head-to-head setting with cryotherapy and placebo.[7] This was a randomized, controlled, multicentre clinical trial and all patients had AK lesions > 5 mm in diameter located on the face or scalp. Of the lesions, 89% underwent a whole cycle of MAL-PDT (two sessions, 7 days apart), while 11% of lesions received only one session. Lesion response was defined as a complete response to treatment at 3 months, on an intent-to-treat basis. Complete response means complete disappearance of the lesion, both visually and on palpation. Partial responders were classified as nonresponders.

For use in the model, the parameter 'percentage of responding lesions' is not adequate. Rather, data on a patient level should be used. Indeed, a patient will not be satisfied with treatment if < 100% of his/her lesions are responding. Such a patient will thus return for second-line treatment.

Table 1 shows the percentage of patients with 100% of lesions responding. Second-line response data are calculated by assuming a mix of possible therapies and applying a factor of 0·95 to the published first-line results of that considered mix.[9]

The cosmetic outcome was also assessed in this trial. Overall cosmetic outcome was assessed with regard to occurrence of the following signs or symptoms: scarring, atrophy, induration, redness or change in pigmentation. Excellent cosmetic outcome was defined as absence of scarring, atrophy or induration, and no or slight occurrence of redness or change in pigmentation compared with adjacent skin. This cosmetic assessment was only made in patients with complete response, i.e. patients in whom 100% of the lesions responded. In AK, 83% of patients treated with MAL-PDT and 51% of those treated with cryotherapy obtained an excellent cosmetic result.

In BCC, two large, multicentre phase III trials (prospective, open, randomized, comparative, multicentre studies) have been undertaken in which MAL-PDT was compared head-to-head with (i) simple surgical excision and (ii) cryosurgery. The first study[8] was performed in six European countries and included primary nBCC lesions which were suitable for simple excision surgery. The second study[10] was performed in seven European countries and included primary sBCC lesions suitable for cryosurgery. For both studies, most patients belonged to TNM stage I (T1N0M0). Only a few patients belonged to TNM stage II (T2N0M0) (see Table 2). Therefore, no subanalyses were performed for these categories in terms of cost-effectiveness ratios.

In the study of Rhodes *et al.*,[8] each patient received a cycle of two sessions, followed, 3 months later, by a second cycle in some if response was not complete (the latter was the case in 27% of patients). In the study of Basset-Séguin *et al.*,[10] on sBCC, each patient received one treatment session, followed,

Table 1 Patients with all lesions responding

	Patients	Lesions		n	Patients with all lesions responding
AK[7]					
MAL-PDT	88	360			71 (80·7%)
Cryotherapy	89	421			51 (57·3%)
Nodular BCC[8]					
MAL-PDT	52	55			45 (86·5%)
			Stage I (T1N0M0)	53	
			Stage II (T2N0M0)	2	
Excision	49	55			46 (93·9%)
			Stage I (T1N0M0)	50	
			Stage II (T2N0M0)	3	
			Data missing	2	
Superficial BCC[10]					
MAL-PDT	62	114			55 (88·7%)
			Stage I (T1N0M0)	97	
			Stage II (T2N0M0)	17	
Excision[a]	62	105			58·8 (94·9%)
			Stage I (T1N0M0)	89	
			Stage II (T2N0M0)	16	

AK, actinic keratosis; BCC, basal cell carcinoma; MAL-PDT, methyl aminolaevulinate-based photodynamic therapy. [a]Adjusted. Sources: Freeman *et al.*,[7] Rhodes *et al.*[8] and Basset-Séguin *et al.*[10]

Table 2 Costs of initial, second-line and follow-up management in cases of actinic keratosis (AK) and basal cell carcinoma (BCC)

	AK	BCC
Initial management with cryotherapy and surgery		
Total cost	€72·10	€148·40
Nonresponse – second-line management		
Total cost	€116·04	€260·80
Recurrence – second-line management		
Total cost	–	€236·90
Follow-up management		
A. Excellent cosmetic outcome		
Total cost	€13·54	€42·8
B. Nonexcellent cosmetic outcome		
Total cost	€44·35	€97·90

3 months later, by a cycle of two sessions in some if response was not complete (as was the case in 32% of patients).

The efficacy of the comparator treatments, excision and cryosurgery, was derived directly from the comparator arms in the respective studies. However, as the study of Rhodes *et al.*[8] was conducted in nodular lesions, the excision response rate may underestimate the overall response rate likely to be achieved in a typical population of nodular and superficial lesions. Similarly, the cryosurgery response in the study by Basset-Séguin *et al.*[10] is likely to be slightly overestimated, as it was conducted in superficial lesions only. For the same reason, and as expected, the response rate to MAL-PDT in nodular lesions (87·3%) was lower than in superficial lesions (94·7%).

The most important comparator of interest is excision as this is currently the method by far the most used in BCC. In order to predict the success rate of excision if it had been an arm in the study by Basset-Séguin *et al.*[10] (sBCC), we applied a method published by Choi *et al.*[11] This method takes the net efficacy of a treatment into account. The net efficacy is the ratio between the difference with the comparator and the total potential improvement that can be obtained.

The resulting numbers of patients in whom 100% of the lesions responded are shown in Table 1. Cosmesis was assessed in both BCC studies. An excellent outcome was obtained in 43% of patients after MAL-PDT and in 7% after excision. The recurrence rate after excision for primary BCC has been reported as 10·1% after a period of 5 years.[12] With MAL-PDT, Soler *et al.*[13] reported a recurrence rate of 11% over a follow-up period of 3 years. This figure was linearly extrapolated in the model to simulate the 5-year recurrence with MAL.

Medical resource use and costs of current treatment

A Delphi panel was organized, consisting of a two-round written questionnaire by mail.[14] Questions were related to current medical practice, the modalities and administration of drugs, examinations, monitoring, the management of adverse events and the management of failure. Twelve Belgian dermatologists participated in this two-round process.

As initial management for AK, cryotherapy was reported in 93·5% of the patients. This justifies the use of this treatment option as comparator for MAL-PDT. If there was no clinical lesion response after initial management, the decision to start second-line management was made on average after 6·9 weeks. In many of the patients, a new treatment with cryotherapy is performed (49·1%), followed by excision surgery (20·5% of the patients), curettage (13·0%) and electrosurgery (11·8%).

In case of a clinical response after treatment of AK (first-line and/or second-line treatment), and excellent cosmetic outcome as experienced by the patient, a follow-up by the dermatologist was still performed. In case of a clinical response after treatment of AK (first-line and/or second-line treatment), with unsatisfactory cosmetic outcome experienced by the patient (nonexcellent cosmetic outcome), some patients may be referred to a plastic surgeon, and additional interventions may be necessary.

As initial management for BCC, surgical excision was reported in 82·3% of the patients. If lesion response was incomplete after initial management with surgical excision, second-line management may be initiated. Second-line management included re-excision (44·4%), Mohs surgery (42·8%), radiotherapy (9·5%) and electrosurgery (3·3%). In cases of recurrence after initial response, second-line management was very similar to treatment in case of nonresponse.

Details of all resource use consumption are available upon request. Unit costs for interventions and investigations and medical visits used in the model were derived from the official listings of the Belgian Health Insurance RIZIV/INAMI (2002). Unit costs for medication were based on the official listings of the RIZIV/INAMI (2002). The total cost of medical resource use was calculated as the unit cost multiplied by the number of tests, investigations and interventions performed. Table 2 shows the average cost of first-line, second-line and follow-up management in cases of AK and BCC.

Cost of methyl aminolaevulinate-based photodynamic therapy

The unit cost of MAL cream per treatment (first-line, second-line treatment) for AK and BCC was based on the average treatment area registered in the multicentre phase III clinical trials.[7,8,10] The analysis takes into account a cost of €290 per 2-g tube MAL cream ex-factory, and a 100% reimbursement. A dose of 1 mg mm^{-2} is required. An overall weighted cost of €182·77 per treatment for AK was found. For BCC (differentiation between nBCC and sBCC was made), a total treatment cost of €182·32 was found for nBCC and a total cost of €129·83 for sBCC.

Sensitivity analysis

A probabilistic multiway sensitivity analysis was applied. That means that all input variables that show uncertainties are

considered together in the model as stochastic variables. We applied binomial distributions for the probabilities of response, and costs in case of nonresponse, costs in case of recurrence and follow-up costs were varied between a minimum (i.e. base case − 20%) and a maximum (i.e. base case + 20%), using a triangular distribution. The model was then run 1000 times, whereby each time, for all stochastic input variables, a figure is taken at random according to the distribution of that variable.[15]

Results

Based on the total cost per year and the effects expressed as percentage of patients with a clinical response and an excellent cosmetic outcome, after a period of 1 year (or 5 years for BCC), the cost-effectiveness ratio was calculated. The results are shown in Table 3. In AK, MAL-PDT is a more expensive treatment compared with cryotherapy; however, the cost per full responder is comparable with cryotherapy (€379·20 and €363·20, respectively). The incremental cost per full responder is €401·10. Monte Carlo evaluation (see figures in brackets in Table 3) reveals that MAL is statistically more expensive than cryotherapy, and that the 95% confidence interval around the incremental cost-effectiveness ratio lies between €290·40 and €596·50 per full responder. This ratio is not statistically different from the currently obtained results with cryotherapy. For nBCC, the incremental cost per full responder is €468·60. For sBCC, the results are similar. The incremental cost per full responder is €251·20. In both cases (nBCC and sBCC) MAL is significantly more expensive than the comparator, but requires a significantly lower cost per full responder compared with current therapy.

Discussion

Our study describes the economic evaluation of MAL-PDT in AK and BCC. A model approach was considered because clinical studies, even if they follow patients for sufficient time, omit to follow up patients who have failed on therapy and need second-line management, and they do not measure medical resource use in cases of success and failure. A model approach also has disadvantages, in that data from different studies are to be combined in the framework. This may lead to uncertainties, which were assessed by applying a probabilistic sensitivity analysis surrounding the base case results.

Taking into account response rates, possible recurrence and cosmetic outcome on the one hand and the costs of nonresponse, recurrence and nonexcellent cosmetic outcome on the other hand, we found in AK that the incremental cost per full responder is €401·10. This seems to be an acceptable result, but comparison with data from other economic evaluations is difficult. One way to interpret the results better is to express them in cost per day in good response or cost per symptom-free day. For instance, in a different area (gastroenterology), the overall average cost per symptom-free day in the acute management of oesophagitis was U.S. $7·88 in an omeprazole group and $10·81 in a ranitidine/metoclopramide group.[16] In our study, the cost per full responder could be translated into a cost per day in response, by assuming that responders experience a good result on average after 3 months and spend the rest of the year ($0{\cdot}75 \times 365 = 274$ days) in good response. The resulting cost per day in good response would be $401{\cdot}10/274 = €1{\cdot}46$. Obviously a comparison would only be complete if a symptomatic day in oesophagitis is comparable with a 'symptomatic' day in AK, a question that can only

Table 3 Overview of costs, effects and incremental cost-effectiveness ratio in treatment of actinic keratosis (AK) and basal cell carcinoma (BCC) (95% confidence intervals are given in parentheses)

	Comparator[a]	MAL-PDT	Incremental cost-effectiveness ratio
AK			
Total cost	€152·90 (134·40–170·70)	€277·30 (267·10–289·30)	
Total effect (probability of response)	0·424	0·729	
Cost-effectiveness ratio = cost per full responder[b]	€363·20	€379·20	€401·10 (290·40–596·50)
Nodular BCC (T303/99)			
Total cost	€280·70 (251·00–309·10)	€402·80 (382·00–423·10)	
Total effect (probability of response)	0·0738	0·3315	
Cost-effectiveness ratio = cost per full responder[b]	€3803·00	€1209·70	€468·60 (€325·60–715·50)
Superficial BCC (T304/99)			
Total cost	€278·30 (248·40–307·30)	€345·20 (326·90–367·20)	
Total effect (probability of response)	0·0737	0·3377	
Cost-effectiveness ratio = cost per full responder[b]	€3797·80	€1022·00	€251·20 (143·70–422·00)

[a]The comparator was cryotherapy in the case of AK and excision in the case of both nodular and superficial BCC. [b]Due to rounding the cost-effectiveness ratios may differ slightly.

be resolved through generic quality of life (QoL) assessments. Interestingly, in Australia, a willingness-to-pay survey[17] demonstrated a high preference ratio associated with the avoidance of scarring. In fact, the scarring and suboptimal cosmetic outcome were considered by patients to be more important even than lesion response, and affected their QoL and willingness to pay more than response. Therefore, it seems that money spent on MAL-PDT is well spent as it offers value to patients at an acceptable cost.

Yet, expressing the effects in number of days with response is also suboptimal. Indeed, the impact of the cosmetic outcomes on QoL (especially the psychological and social dimensions) should ideally be expressed and applied in health economic evaluations such as ours. It is recommended to collect this type of data, applying generic QoL instruments in order to make results comparable with results in other disease areas.

In BCC, the above issue is less relevant, because even without interpreting the data in terms of days with response, the cost per responder is lower with MAL-PDT compared with excision surgery. This allows us to draw the conclusion that MAL-PDT is value for money in this indication.

In conclusion, the results of this model suggest that MAL-PDT is a cost-effective intervention in AK, taking a 1-year time horizon, if society is willing to pay ± €1·50 per day of response, whereby response is expressed as clinical response plus excellent cosmetic outcome, and that MAL-PDT is better value for money than excision in BCC, taking a 5-year time horizon.

References

1 Drake LA, Ceilley RI, Cornelison RL *et al.* Guidelines of care for actinic keratoses. *J Am Acad Dermatol* 1995; **32**:95–8.

2 Szeimies RM, Karrer S, Radakovic-Fijan S *et al.* Photodynamic therapy using topical methyl 5-aminolevulinate compared with cryotherapy for actinic keratosis: a prospective, randomized study. *J Am Acad Dermatol* 2002; **47**:258–62.

3 Salasche SJ. Epidemiology of actinic keratoses and squamous cell carcinoma. *J Am Acad Dermatol* 2000; **42**:S4–7.

4 Frost CA, Green AC. Epidemiology of solar keratoses. *Br J Dermatol* 1994; **131**:455–64.

5 Streit M. Basal cell carcinoma, general information. (http://www.photocure.com/professionals/), last accessed 19 June 2006.

6 Belgisch Kankerregister. Tables, incidence year 1997, tumours per localisation and per age category. (http://www.kankerregister.org/), last accessed 19 June 2006.

7 Freeman M, Vinciullo C, Francis D *et al.* A comparison of photodynamic therapy using topical methyl aminolevulinate (Metvix) with single cycle cryotherapy in patients with actinic keratosis: a prospective, randomized study. *J Dermatolog Treat* 2003; **14**:99–106.

8 Rhodes LE, de Rie M, Enstrom Y *et al.* Photodynamic therapy using topical methyl aminolevulinate vs surgery for nodular basal cell carcinoma: results of a multicenter randomized prospective trial. *Arch Dermatol* 2004; **140**:17–23.

9 Silverman MK, Kopf AW, Grin CM *et al.* Recurrence rates of treated basal cell carcinomas. Part 1: overview. *J Dermatol Surg Oncol* 1991; **17**:713–18.

10 Basset-Séguin N, Ibbotson S, Emtestam L *et al.* Photodynamic therapy using methyl aminolevulinate is as efficacious as cryotheraphy in superficial BCC, with better cosmetic results: results of a European randomized and multicenter study. *J Dermatolog Treat* 2004; **15**:266 (Abstr).

11 Choi H, Seeger J, Kuntz K. A cost-effectiveness analysis of treatment options for methotrexate-naïve rheumatoid arthritis. *J Rheumatol* 2002; **29**:1156–65.

12 Rowe DE, Carroll RJ, Day CL Jr. Long-term recurrence rates in previously untreated (primary) basal cell carcinoma: implications for patient follow-up. *J Dermatol Surg Oncol* 1989; **15**:315–28.

13 Soler AM, Warloe T, Berner A *et al.* A follow-up study of recurrence and cosmesis in completely responding superficial and nodular basal cell carcinomas treated with methyl-5-aminolaevulinate-based photodynamic therapy alone and with prior curettage. *Br J Dermatol* 2001; **145**:467–71.

14 Evans C. The use of consensus methods and expert panels in pharmacoeconomic studies. Practical applications and methodological shortcomings. *Pharmacoeconomics* 1997; **12**:121–9.

15 Briggs AH, Mooney CZ, Wonderling DE. Constructing confidence intervals for cost-effectiveness ratios: an evaluation of parametric and non-parametric techniques using Monte Carlo simulation. *Stat Med* 1999; **18**:3245–62.

16 Bloom BS, Hillman AL, LaMont B *et al.* Omeprazole or ranitidine plus metoclopramide for patients with severe erosive oesophagitis. A cost-effectiveness analysis. *Pharmacoeconomics* 1995; **8**:343–9.

17 Weston A, FitzGerald P. Discrete choice experiment to derive willingness-to-pay for methyl aminolevulinate photodynamic therapy versus simple excision surgery in basal cell carcinoma. *Pharmacoeconomics* 2004; **22**:1195–208.