

COST-EFFECTIVENESS ANALYSIS OF 4% FLUOROURACIL FOR THE TREATMENT OF ACTINIC KERATOSIS IN THE CZECH REPUBLIC

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Value Outcomes

Background

4% fluorouracil (4-FU) is commonly used in accordance with SmPC for the treatment of actinic keratosis (AK). Despite its widespread use, there is no published pharmacoeconomic model describing the 4-FU in the literature or specifically in the Czech Republic (CZE).

Objectives

Clinical evidence suggests that 4-FU provides benefit in complete clearance of AK¹. Our aim was to assess cost-effectiveness of 4-FU in the treatment of AK in comparison with cryotherapy in CZE as cryotherapy was the main comparator in local clinical practice.

Table 1. Decision tree settings

Analysis type and model	Cost-utility analysis, Decision tree
Software	Microsoft Excel
Perspective	Healthcare payers' (health insurance funds)
Time horizon	24 months (2 years)
Discount rate	3 % for costs and outcomes (> 1 year)
Assessed intervention	Tolak (4% fluorouracil)
Comparator	Cryotherapy
Population	Population based on current indication criteria
Efficacy data	Dohil et al. ¹ , SmPC 4% fluorouracil ⁶ , previous pharmacoeconomic analyses ⁷
Outcomes	Quality-adjusted life-years (QALY)
Sensitivity analysis	Scenario analysis, probabilistic sensitivity analysis
Mortality	Mortality was not taken into consideration based on short time horizon and character of disease

Table 2. Probability of complete clearance (100% clearance)

Treatment	100% clearance (1 st line)	100% clearance (2 nd 3 rd line)
4% fluorouracil ¹	54.4 %	54.4 %
Cryotherapy ⁷	11.0 %	11.0 %

Table 3. Probability of recurrence of actinic keratosis

Treatment	Probability of recurrence of actinic keratosis
4% fluorouracil ⁶	54.9 %
Cryotherapy ^{8,9}	72.0 %

Table 4. Probability of retreatment in case of treatment failure or recurrence actinic keratosis

Treatment	Probability of retreatment in case of treatment failure	Probability of retreatment in case of recurrence
4% fluorouracil	83 % ¹⁰	61 % ⁷
Cryotherapy	61 % ⁷	61 % ⁷

Table 5. Costs

Item	Costs
4% fluorouracil (20 g package)	77.12 €
Cryotherapy	32.28 €
Dermatovenerology visit	16.53 €
Dermatovenerology visit (control)	5.58 €
Adverse events – topical corticosteroids	2.87 €

Table 6. Utility values

Health state	Utility values
Without actinic keratosis (successful treatment)	1.000*
With actinic keratosis (unsuccessful treatment, recurrence)	0.986**

*Assumption representing complete health

**Average of published values Littenberg et al.¹¹ and Chen et al.¹²

Table 7. Base case results of cost-effectiveness analysis

	4% fluorouracil	Cryotherapy	Increment
Total costs (€)	158.07 €	115.36 €	42.71 €
Terminal state 1	18.01 €	0.65 €	17.36 €
Terminal state 2	15.09 €	5.15 €	9.94 €
Terminal state 3	11.36 €	2.07 €	9.33 €
Terminal state 4	23.93 €	2.03 €	21.90 €
Terminal state 5	37.93 €	7.26 €	30.67 €
Terminal state 6	21.09 €	5.76 €	15.37 €
Terminal state 7	17.69 €	46.49 €	-28.80 €
Terminal state 8	5.39 €	22.96 €	-17.52 €
Terminal state 9	7.54 €	23.04 €	-15.45 €
Total QALY	1.9532	1.9433	0.0100
Terminal state 1	0.1943	0.0104	0.1838
Terminal state 2	0.1623	0.0841	0.0782
Terminal state 3	0.2278	0.0604	0.1673
Terminal state 4	0.4798	0.0606	0.4192
Terminal state 5	0.4035	0.1172	0.2863
Terminal state 6	0.1523	0.0635	0.0888
Terminal state 7	0.1263	0.5082	-0.3819
Terminal state 8	0.0568	0.3654	-0.3086
Terminal state 9	0.1503	0.6736	-0.5232
ICER (€/QALY)			4,271 €/QALY

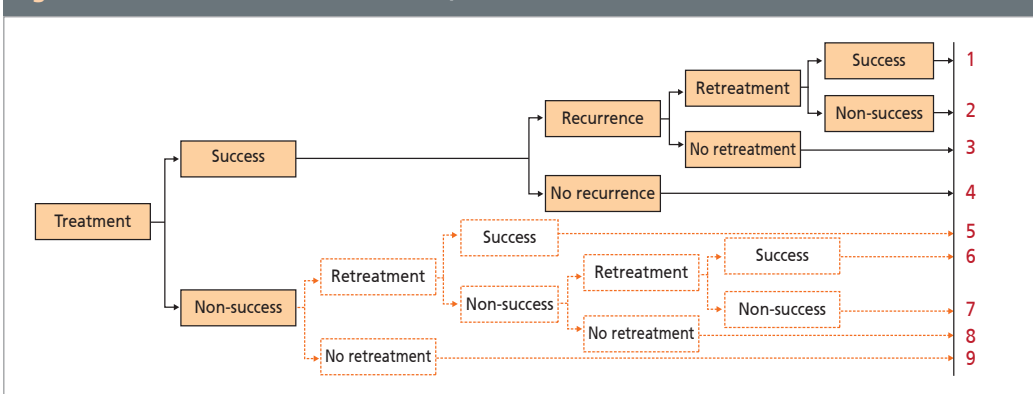
Table 8. Setting of PSA

Parameter	Distribution
Probabilities- success, non-success, retreatment, no retreatment, recurrence, no recurrence	Beta
Utility – health state with actinic keratosis	Beta
Costs	Gamma

References

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Figure 1. Model structure - decision tree, terminal states



Methods

We developed a two-year decision tree model (Table 1). The model comprises six possible states: 1) success, 2) non-success, 3) recurrence, 4) no recurrence, 5) retreatment, and 6) no retreatment allowing to undergo first, second and third line of treatment depending on subsequent health state (Figure 1). In total, there are nine possible terminal health states when combining six possible states including following lines of treatment (Figure 1).

Direct evidence of probability of success of cryotherapy vs. 4-FU was not available from published literature. It was calculated combining published probability of complete clearance for 4-FU and odds ratio (OR, cryotherapy versus 5% fluorouracil) in published network meta-analysis (NMA)². Clinical evidence suggests non-inferiority efficacy of 4% and 5% fluorouracil. Probability of success in 4-FU arm was based on published clinical trial (Table 2). Probabilities of other health states were derived from published clinical trials or relevant evidence (Table 3, Table 4).

The model projects quality-adjusted life-years (QALYs) and costs from healthcare payers' perspective. Costs were based on actual list prices and reimbursement tariffs, and resource use from previous pharmacoeconomic analyses as of 2015/2016 recalculated to actual prices as of 2021 (i.e. the year of submission to local HTA agency) (Table 5). Utilities were derived from the published literature (Table 6). Costs and outcomes were discounted by 3%. Results were evaluated at the Czech willingness-to-pay (WTP) threshold is equal to ≈ €48,600 (1.2 mil CZK) (Table 7)³. Costs were recalculated from Czech crowns (CZK) to EUR (€) using exchange rate as of Q1/2022 equal to 24.653⁴.

The uncertainty in the model was assessed using probabilistic sensitivity analysis (PSA), inputs are shown in Table 8, one-way sensitivity analysis and scenario analysis.

Table 9. Detailed breakdown of probabilities, costs and QALYs for every terminal health state

	4% fluorouracil			Cryotherapy		
	Probability	Costs (€)	QALY	Probability	Costs (€)	QALY
Terminal state 1	0.0991	181.64 €	1.960	0.0053	120.15 €	1.962
Terminal state 2	0.0831	181.64 €	1.953	0.0430	120.15 €	1.955
Terminal state 3	0.1165	97.55 €	1.955	0.0309	66.36 €	1.957
Terminal state 4	0.2453	97.55 €	1.955	0.0308	66.36 €	1.966
Terminal state 5	0.2059	184.16 €	1.960	0.0597	121.77 €	1.962
Terminal state 6	0.0779	270.76 €	1.954	0.0324	177.18 €	1.958
Terminal state 7	0.0653	270.76 €	1.933	0.2623	177.18 €	1.937
Terminal state 8	0.0293	184.16 €	1.936	0.1884	121.77 €	1.939
Terminal state 9	0.0775	97.55 €	1.939	0.3471	66.36 €	1.941
Weighted average*	1.0000 ¹	158.07 €	1.953	1.0000 ¹	115.36 €	1.943

*costs/QALY are weighted by probability of a given terminal state; ¹Sum of probabilities

Figure 2. Cost-effectiveness scatter plot

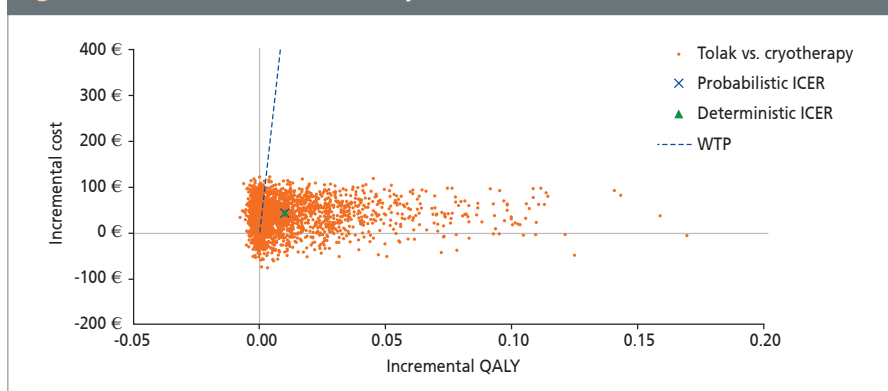
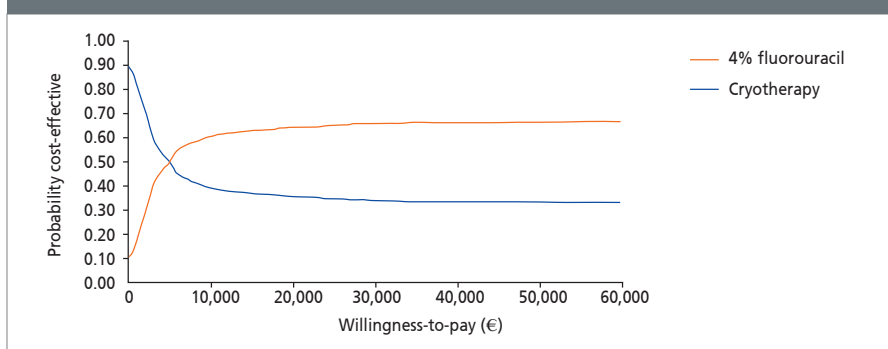


Figure 3. Cost-effectiveness acceptability curve



Results

Over a two-year time horizon, 4-FU yields additional 0.0100 QALY (1.9532 vs. 1.9433) at the additional total costs of €42.71 (€158.07 vs. €115.36) compared with cryotherapy, with the incremental cost-effectiveness ratio of €4,271 (Table 7). Detailed breakdown of probabilities, costs and QALYs in all health states is shown in Table 9.

PSA (3,000 interactions) showed that 4-FU is cost-effective with probability of 66.4 % at the WTP (Figure 2, Figure 3). Scenario sensitivity analyses were also performed while the most impactful model parameters were: 1) costs of 4-FU, 2) consumption of 4-FU per day, 3) same probability of retreatment for recurrence and treatment failure.

Conclusions

4-FU is a cost-effective therapy for patient with AK. Sensitivity analyses confirmed the robustness of the base-case results. Based on the presented analysis, 4-FU (Tolak) received positive assessment of local Czech HTA agency (State Institute for Drug Control, SUKL)⁵ and consequently entered the reimbursement system in CZE. 4-FU is now available to patients with AK who need it and extends currently limited therapeutic options in AK. To our knowledge, this is a first published cost-effectiveness analysis of 4-FU in the literature.

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