Cost-utility analysis of pegaspargase for the treatment of acute lymphoblastic leukemia in Greece.

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Introduction

- Acute lymphoblastic leukemia (ALL) is an acute, rapidly progressing and life-threatening form of cancer involving immature lymphocytes called lymphoblasts. [1].
- The treatment of ALL includes long-term use of multiagent chemotherapy [2], of which asparaginase is a cornerstone component [2, 3].
- Asparaginase is an enzyme derived from bacteria that deaminates circulating asparagine and glutamine [4] and is commonly available in different forms such as the L-Asparaginase derived from Escherichia coli, a product isolated from Erwinia chrysanthemi i.e., Erwinia Asparaginase and a pegylated form of this enzyme, pegaspargase.
- Historically, native Asparaginase was used as the first-line standard of care Asparaginase for patients with ALL. However, due to short half-life of native Asparaginase, frequent injections are needed and hypersensitivity reactions are associated with this treatment occurred in 20-40% of ALL patients [5, 6].
- Pegaspargase provides comparable efficacy to available treatment options, with a lower administration frequency, and a decreased incidence of hypersensitivity reactions [5, 7-10].
- Nonetheless, as healthcare systems are required to allocate the available resources efficiently in order to maximize health benefits, clinical data need to be also supported by economic evidence. This is especially true in countries where decisions regarding pricing and reimbursement are based on scientific evidence of health technology assessment.

Objective

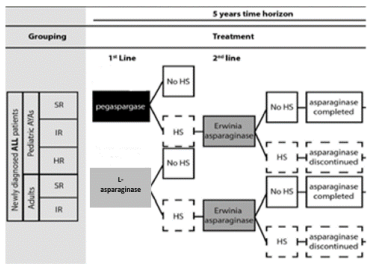
To assess the cost-utility of pegaspargase versus L-Asparaginase, both followed by Erwinase in the therapy sequence, as treatment option for pediatric, adolescents and adult patients with ALL in Greece.

Methods (1/2)

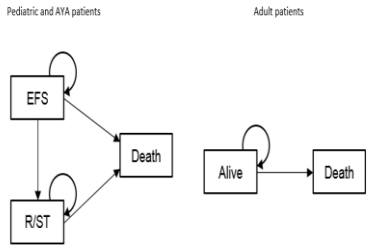
- A published cost-utility model [11] comprised a decision tree (DT) and a state-transition Markov model was locally adapted from public payer perspective to compare a treatment sequence with pegaspargase to a sequence with L-asparaginase.
- The DT model included treatment regimen cycles, and potential hypersensitivity to asparaginase. As patients experience a survival outcome during and after treatment, a Markov model was also incorporated in parallel to extrapolate over a life-time horizon (Figure 1).

Figure 1. Models' structure

A. Decision Tree model structure



B. Markov model structure



EFS, event-free survival; R/ST, relapse/secondary tumour. AYA, Adolescents and young adult
Source: Adopted from HU et al. [11]

- The target population of the model considers two separate patient groups. Pediatric and adolescence and young adult (AYA) patients, aged ≤25 years (split into high-risk (HR), intermediate-risk (IR) and standard-risk (SR) patients). Adult patients aged from 26 to 65 years (split into those aged ≤40 years and those aged ≥41 years and those eligible or not for transplant) (Table 1).
- For pediatric patients, 5-year Overall Survival (OS) and event-free survival (EFS) for SR, IR and HR groups, were extracted from published studies [9, 10] and a reduction of 5% was assumed for both EFS and OS, due to hypersensitivity [11].

Methods (2/2)

- For adults patients, due to lack of available data, it was assumed that EFS = OS according to published study [11]. The 5-year OS was 40% for patients ≤40 years and 30% for patients ≥41 years. Also, a reduction of 5% was assumed for OS, due to hypersensitivity [11].
- The risk of hypersensitivity leading to a treatment switch was for first and second- line asparaginase therapy for each of the asparaginase formulations were extracted from published studies [12-15] and validated from local experts (Table 1).

Table 1. Patients characteristics and hypersensitivity data used in the model

Parameters	Pediatric & AYA			Adults		Source
Population distribution (%)	75%			25%		Local experts
	HR	IR	SR	Aged ≤ 40y	Aged ≥41 y	
Risk/age group (%)	13%	66%	21%	30%	70%	
Eligible for transplant (%)		-		50%	50%	
Median age		7 years		31 years	53 years	Local experts
BSA		0.999			1.790	
Risk of hypersensitivity						
First-line treatment	Risk of hypersensitivity			Source		
Pegaspargase	3.6%			Local experts		
Native asparaginase	20%			Place et al. 2015 [14], Pieters et al. 2011 [13] and Local experts		
Second-line treatment	Risk of hypersensitivity			Source		
Erwinase	37%			Vrooman et al. 2016 [15] and Local experts		

AYA, Adolescence and Young Adult; BSA, Body Surface Area; HR, high-risk; IR, intermediate-risk; SR, standard-risk; y, years.

- Utility values were taken from published studies [16, 17].Moreover, a utility decrement of 0.014 was applied to reflect the impact of hypersensitivity on patient health-related quality of life [18], while patients who were in the relapse/secondary malignancy (R/ST) state could not transition to the EFS state and were given a decreased utility of 20%.
- Cost inputs considered in the model include drug acquisition, administration, and management of hypersensitivity (Table 2). All costs reflect the year 2020 in euro.

Table 2. Cost inputs considered in the model

	Unit cost (€)	Source
Drug acquisition cost		
Pegaspargase 3,750 IU/vial x 1vial	1,540	Greek Ministry of Health [24]
L-asparaginase 10,000 IU/vial x 1 vial	339	Pharmaceutical Research and Technology Institution [25]
Erwinase 10,000 IU/vial x 5 vial	4,411	
Administration cost		
Pegaspargase 3,750 IU/vial x 1vial	670	Local experts, and DRG (Code: Σ22X) [26]
L-asparaginase 10,000 IU/vial x 1 vial	970	Local experts, and DRG (Code: Σ22M) [26]
Erwinase 10,000 IU/vial x 5 vial		
Hypersensitivity costs	697	Local experts, DRG (Code: Φ61A, P22M) [26], Drug price bulletin [24], Gourzoulidis et al. 2017 [27] and the official website of EOPYY

DRG, Diagnostic Related Groups

- Asparaginase forms the backbone of chemotherapeutic regimens used in current clinical practice. As different types of asparaginase are being compared in the current model, with the remainder of the chemotherapeutic regimen unaltered, hence, only costs associated with the asparaginase were modelled.
- A willingness to pay (WTP) threshold of €54,000 per quality-adjusted life year (QALY) was used in the current analysis, based on the literature which reported that a health intervention should be considered as cost-effective, if the ICER is between one to three times the gross domestic product (GDP) per capita of that country [19-22].
- The Greek GDP per capita was taken from the International Monetary Fund (IMF), which estimated it at €18,000 using current prices [23].
- Primary outcomes were patients' QALYs, total costs and incremental cost-effectiveness ratio (ICER) per QALY gained.
- Costs and outcomes that occurred beyond one year were discounted at a 3.5% annual rate which is the standard practice in Greece [24, 25].
- A deterministic sensitivity analysis (DSA) was undertaken to identify the parameters to which the model results was most sensitive.
- A probabilistic sensitivity analysis (PSA) was conducted to account for uncertainty in the model.

Acknowledgments

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Results

- The total cost for the treatment sequence with pegaspargase and sequence with a L-Asparaginase was estimated to be €5,652 and €7,350, respectively (Table 3).
- In terms of health outcomes, the analysis showed that pegaspargase sequence was more effective than L-asparaginase sequence (18.12 vs 18.07 QALYs) (Table 3).
- The sequence with pegaspargase appears to be a cost-saving treatment option over sequence with L-asparaginase (-€1,698) with additional QALYs of 0.05 (Table 3), indicating that sequence with pegaspargase was a dominant treatment strategy compared to sequence with L-asparaginase (Table 3).

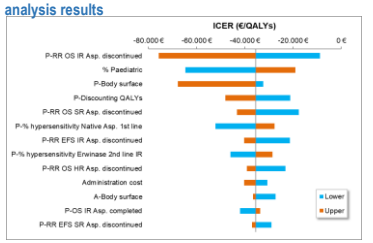
Table 3. Base-case model results

Breakdown cost	Sequence with Pegaspargase	Sequence with L-asparaginase	Incremental
Treatment cost	€4,644	€4,647	-€3
Administration cost	€969	€2,514	-€1,54
Hypersensitivity	€39	€189	-€150
Total costs	€5,652	€7,350	-€1,698
QALYs	18.12	18.07	+0.05
ICER per QALY gained			Dominant

ICER, Incremental cost–effectiveness ratio; QALYs, Quality-adjusted life years; Dominant (improve outcomes in terms of QALY with reduced total cost).

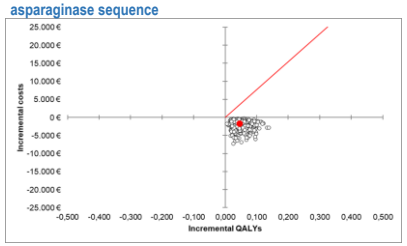
- The results of DSA indicated that the relative risk of OS in intermediate risk of pediatric and AYA population (for L-asparaginase discontinuation) was the parameter with the greatest effects on the ICER (Figure 2).
- PSA confirmed the deterministic results, showed that pegaspargase had a probability of 100% of being a cost-effective option compared to sequence with L-asparaginase, at a WTP threshold of €54,000. After PSA was run for 1,000 simulations, the incremental gains in terms of QALYs were plotted against the incremental costs of pegaspargase versus L-asparaginase sequence on the cost-effectiveness plane (Figure 3).

Figure 2. Tornado diagram of deterministic sensitivity analysis results



EFS, event-free survival; HR, high-risk; ICER, Incremental cost–effectiveness ratio; IR, intermediate-risk; OS, Overall Survival; QALY, Quality-adjusted life year; SR, standard-risk.

Figure 3. Cost-effectiveness plane of pegaspargase versus L-asparaginase sequence



QALY: Quality-adjusted life year.

- As for the scenario analyses results, when only the adult population was considered in the analysis, the incremental analysis showed that, compared to sequence with L-ASNase, sequence with PEG had higher QALYs and lower total cost, indicating that sequence with PEG was a dominant treatment strategy compared to sequence with L-ASNase. Similar results were reported, when only the pediatric and AYA population was considered in the model, sequence with PEG was a dominant treatment strategy compared to sequence with L-ASNase (Table 4).

Table 4. Cost effectiveness scenario analyses results

Breakdown cost	Sequence with Pegaspargase	Sequence with L-asparaginase	Incremental
Scenario analyses			
100% paediatric and AYA population			
Total costs	€8,545	€12,352	-€3,807
QALYs	22.13	22.06	+0.07
ICER per QALY gained			Dominant
100% adult population			
Total costs	€5,913	€13,368	-€7,455
QALYs	3.433	3.428	+0.005
ICER per QALY gained			Dominant

ICER: Incremental cost–effectiveness ratio; QALY: Quality-adjusted life year; Dominant (improve outcomes in terms of QALY with reduced total cost).

Conclusion

This economic evaluation suggests that pegaspargase sequence was found to be less costly and more effective in relation to L-asparaginase sequence, representing a dominant strategic option for Greek public payer in ALL.

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