EE165

Cost-Effectiveness Analysis of Liposomal Formulation of Daunorubicin and Cytarabine (CPX-351) for the Treatment of Adult Patients With Newly Diagnosed Therapy-Related AML or AML With Myelodysplasia-Related Changes in Greece

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Background

- Acute Myeloid Leukemia (AML) is a rare malignancy, defined by International Consensus Classification (ICC) of Myeloid Neoplasms and Acute Leukemias as: ≥20% blasts in the peripheral blood or bone marrow and ≥10% blasts when AML is associated with recurrent abnormalities [1-3].
- AML represents 1% of all cancers and corresponds to incidence less than 6 per 100,000 people in Europe and is generally considered to affect the elderly [4, 5].
- AML can further be characterised clinically into 2 subtypes: therapy-related AML (t-AML), which develops as a complication of prior exposure to cytotoxic therapy and/or radiation, and AML with myelodysplasia-related changes (AML-MRC), which represents a transformation to AML from a prior diagnosis of myelodysplastic syndromes/ myeloproliferative neoplasm or with MDS-related cytogenetic abnormalities [5-7].
- They account for 25% of all AML diagnoses and represent those with the worst prognosis of all AML subtypes with a disease course that is rapidly and highly fatal.
- CPX-351 (daunorubicin and cytarabine) is a cytotoxic combination of daunorubicin and cytarabine in a 1:5 molar ratio encapsulated in liposomes for intravenous administration. CPX-351 delivers a synergistic combination of daunorubicin and cytarabine to leukaemia cells for a prolonged period of time.
- The efficacy and safety of CPX-351 was assessed in a phase 3 clinical trial [8] where it was associated with improved outcomes versus standard intensive chemotherapy (7+3 with cytarabine and daunorubicin) in patients with high-risk AML. Indicatively, CPX-351 was associated with median overall survival of 9.6 months vs 5.9 months with 7+3 (HR=0.69 [95% CI: 0.52, 0.90], P=0.005).
- To investigate how much this clinical benefit that the new technology seems to provide would cost to the public healthcare system compared to current standard of care (SoC), a cost-effectiveness analysis was undertaken which was also used as a tool to support the decision making in the reimbursement of the intervention.

Objective

To assess the cost-effectiveness of CPX-351 versus the SoC which consists of cytarabine and idarubicin, as treatment of adult patients (over 60 years old) with newly diagnosed (ND) t-AML or AML-MRC in Greece.

Methods 1/2

Assumption/ Limitation

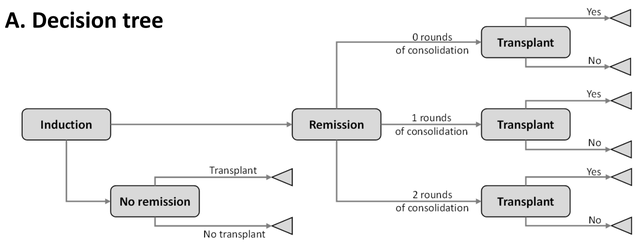
- Since daunorubicin, used as SoC in the clinical trial, was not reimbursed in Greece, idarubicin substituted daunorubicin, adjusted to match equivalent dosing -as suggested by literature- along with cytarabine and considered as SoC in the present analysis [9].

Model structure

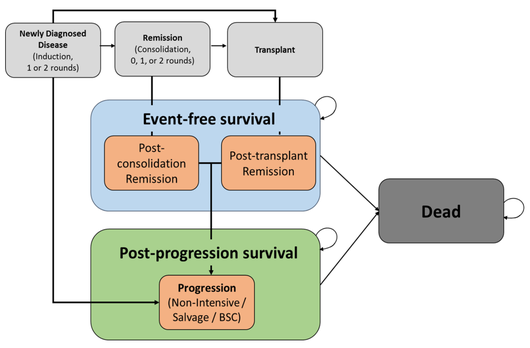
- A hybrid decision tree (DT) with a partitioned survival model (PSM) was locally adapted to reflect the natural progression of adult patients (over 60 years old) with ND t-AML or AML-MRC, over a lifetime horizon (30 years) from the public payer perspective, as shown in Figure 1.
- Patients first enter the model in the ND health state, where they received either one or two rounds of induction therapy. If patients achieved remission, then they could receive up to two rounds of consolidation therapy, after which they may receive a transplant (Figure 1A).
- Patients achieving remission post-induction may relapse after consolidation or transplantation. Patients who do not achieve remission post-induction may progress (receiving *non-intensive therapy*, *salvage therapy*, or *best supportive care*) or receive a *transplant*. Patients may die at any time (Figure 1B).

Figure 1: Model structure

A. Decision tree



B. Partitioned survival model



Model inputs (1/2)

- Baseline patient characteristics such as age, AML type along with clinical inputs were sourced from the clinical study report of the phase 3 trial [8].
- Extrapolation of the survival data beyond the trial period was done by exploring standard parametric fits to the Kaplan-Meier data from the clinical trial, while Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used to choose among different model fittings.

Methods 2/2

Model inputs (2/2)

- Mean weight and body surface as well as the background mortality estimates for Greece were localized according to literature [10,11].
- Health state utilities were sourced from an AML trade-off utility study conducted by Evidera [10].
- The market shares of treatments including non-intensive & salvage therapies were provided by Genesis data on file.
- Unit drug costs were based on the ex-factory prices published in the drug price bulletin [12] issued by the Greek Ministry of Health after also applying the relevant discounts provided in the corresponding legislation. The full list of cost inputs considered in the analysis is illustrated in Table 1.

Table 1. Model cost inputs

Parameter			Cost	Source
Drug acquisition costs	Induction and Consolidation	***Treatment***	***Cost per pack***	Drug price bulletin issued by Greek Ministry of Health [11]
		CPX-351	€ 5,175	
		SoC: Cytarabine	€ 7	
		SoC: Idarubicin	€ 22	
	Non-intensive therapy~	Decitabine	€1,024	
		Midostaurin	€ 12,185	
	Salvage therapy	FLAG-IDA[x]: Fludarabine	€ 105	
		FLAG-IDA[x]: Filgrastim	€ 161	
		HAM[x] Mitoxantrone	€ 36	
		MEC[x] Etoposide	€ 8	
		CLAG-Mov[x] Cladribine	€ 1,634	
Administration cost		***Administration type***	***Unit Cost***	Government gazette [12, 13]
		Outpatient (one-day clinic)	€ 80	
		Inpatient (hospitalization)	€ 72	
AE management costs		Adverse event	Unit Cost	The AE costs were retrieved from available studies concerning the AE management in the Greek healthcare system. All costs were inflated to 2022 values based on the health price indexes issued by Greek statistical authority (ELSTAT) [14]
		Bacteremia	€ 573	
		Diarrhea	€ 73	
		Ejection Fraction Decreased	€ 355	
		Fatigue	€ 46	
		Febrile Neutropenia	€ 803	
		Hypertension	€ 358	
		Hypotension	€ 138	
		Hypoxia	€ 324	
		Pneumonia	€ 980	
		Pulmonary oedema	€ 892	
		Respiratory Failure	€ 271	
		Sepsis	€ 2,316	
Monitoring costs		***Test***	***Unit Cost***	Unit costs were sourced from the official website of EOPYY [15]
		Full blood count	€1.69	
		Platelets	€ 11.01	
		Chemistry panel	€ 43.49	
		Liver function test	€ 5.92	
		Coagulation panel	€ 19.38	
		Bone marrow biopsy	€ 1,000	Calculation based on unit costs from Government gazette [16]
		Blood transfusion	€ 80	Assumption: Cost of one-day clinic, Government gazette [12]
HSCT cost		Procedure	Unit Cost	DRG (Codes: E20A & E07A) [16]
		Pre-transplant procedure	€ 300	
		Stem cells transplantation	€ 17,137	
Follow-up costs		Post consolidation remission	€ 3,076	Vellopoulou et al. 2017 [17] (inflated to 2022 values)
	Post-transplant remission	0-12 months	€ 3,076	
		1-2 years	€ 2,798	

~Non-intensive therapy is constituted by Azacytidine and low-dose cytarabine as well whose costs are illustrated above.

[x]FLAG-IDA: Cytarabine, Idarubicin, Fludarabine, Filgrastim; HAM: Cytarabine, Mitoxantrone; MEC: Cytarabine, Mitoxantrone, Etoposide; CLAG-Mov: Cytarabine, Mitoxantrone, Cladribine, Filgrastim

AE; adverse event; AML; acute myeloid leukemia, HSCT; hematopoietic stem cell transplant, SoC; standard of care,

Data analysis

- Although there is no official willingness-to-pay (WTP) threshold for Greece, a WTP threshold of € 54,000 per QALY was used in the current analysis which equals to three times multiplied by the GDP per capita as sourced from the official website of International Monetary Fund (IMF) [18].
- Primary outcomes were patients' life years (LYs), quality-adjusted LYs (QALYs), total costs and incremental cost-effectiveness ratio (ICER) per LY & QALY gained.
- An annual discount rate of 3.5% was applied to all costs and outcomes occurred beyond first year, as this is the standard practice in Greece [19, 20] as well as in other jurisdictions.
- A deterministic sensitivity analysis (DSA) was undertaken to identify the parameters to which the model results were most sensitive.
- A probabilistic sensitivity analysis (PSA) was conducted to account for uncertainty in the model.

Results 1/2

- The total lifetime cost per patient was estimated to be €62,396 and €20,375 for CPX-351 and SoC treatment arms, respectively.
- In terms of health outcomes, the analysis indicated that that the corresponding per patient LYs for CPX-351 and SoC were 2.44 and 1.60, respectively (increase of 0.84 LYs with CPX-351).
- Further, the lifetime QALYs gained for CPX-351 and SoC were 1.64 and 0.86, respectively (0.78 gain with CPX-351).
- The incremental cost-effectiveness ratios (ICER) of CPX-351 vs SoC were €50,316 and €53,917 per LY and QALY gained, respectively (Table 2).

Results 2/2

- The results of OWSA indicated that the discount rate applied on health and cost inputs over time were the parameters with the greatest impact on the ICER.
- PSA confirmed the deterministic results, showed that CPX-351 had a probability of 64% of being a cost-effective option compared to BSC, at a WTP threshold of €54,000 (Figure 2).
- In the scatter plot below (CEP), each simulated estimate of the expected incremental costs and effects is illustrated. More precisely CEP indicates the expected ICER (cost per QALY gained) of CPX-351 compared to SoC. CPX-351 is expected to be more effective but more costly than SoC. The CEP is located both up and down of the dashed line which represents the predefined WTP threshold, meaning that CPX-351 represents a cost-effective option in approximately half of the 500 simulations (Figure 3).

Table 2. Cost-effectiveness analysis results

	CPX-351	SoC	Incremental
LYs	2.44	1.60	0.84
QALYs	1.64	0.86	0.78
Cost	€ 62,396	€ 20,375	€ 42,021
Incremental cost per LY gained			€ 50,316
Incremental cost per QALY gained			€ 53,917

LYs; Life years, QALYs; Quality adjusted life years, SoC; Standard of Care

Figure 2: Tornado diagram of DSA: CPX-351 vs SoC

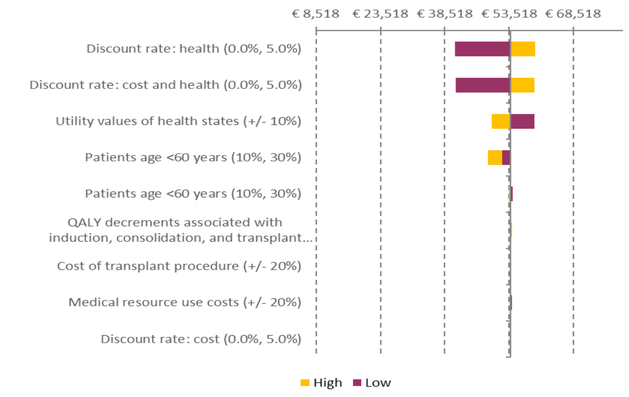
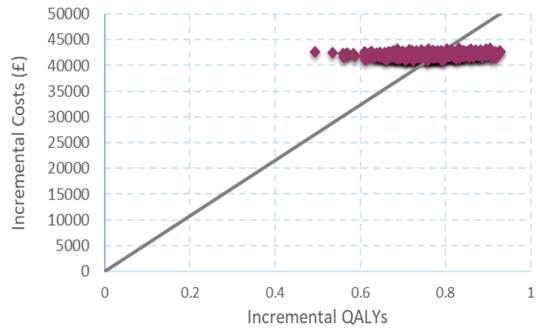


Figure 3: Cost–effectiveness plane of CPX-351 versus SoC



CONCLUSIONS

CPX-351 is a cost-effective option for treating adult patients with ND t-AML or AML-MRC in Greece, providing additional LYs and QALY gains as compared to SoC.

Acknowledgement

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