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Cost-Effectiveness Analysis of Treatment with Defibrotide for Patients with Severe Sinusoidal Obstruction Syndrome

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Abstract: Defibrotide is the only approved pharmacologic therapy for severe sinusoidal obstruction syndrome (SOS), also known as hepatic veno-occlusive disease (VOD), particularly post-hematopoietic stem cell transplantation (HSCT). This comprehensive review summarizes the cost-effectiveness of defibrotide in this critically ill population, comparing it to best supportive care (BSC) using decision analytic models, real-world data, and published literature. Emphasis is placed on economic outcomes, survival benefits, and health system perspectives from Europe and North America.

Keywords: Defibrotide, SOS/VOD, HSCT, cost-effectiveness, survival benefits.

INTRODUCTION

Severe SOS/VOD is a life-threatening complication following HSCT, characterized by hepatic dysfunction and multi-organ failure, with reported mortality rates exceeding 80% under supportive care. Only defibrotide has demonstrated survival benefit in randomized trials and observational studies, prompting evaluation of its considerable costs relative to improved outcomes.

Cost-effectiveness analyses, particularly in rare diseases where randomized trials may be impractical, model both direct treatment expenses and downstream clinical and economic impacts, such as reduced hospital/ICU stay and increased survivorship.

METHODS OVERVIEW

Economic models for defibrotide typically employ a Markov structure composed of:

- An acute phase (often 1-year) modeling immediate outcomes post-transplant
- A long-term phase estimating survival and quality-adjusted life years (QALYs) among responders

Cost inputs include drug acquisition, administration, hospitalization, ICU utilization, and follow-up. Effectiveness measures are life-years (LYs), QALYs, and overall survival rates. Perspectives adopted in published analyses range

from national health systems (Spain, Canada) to US transplant center budgets. Direct comparison to BSC is the analytic standard.

Clinical Effectiveness

- **Survival Benefit:** Phase III trial and cohort data indicate that defibrotide increases 100-day survival by 23% compared to historical controls (from ~38% to 61%)[1].
- **Complete Response Rate:** Meta-analyses report rates of 30-40%, with 100-day survival rates up to 60%[2][3].
- **Hospital Stay:** Defibrotide reduces ICU and overall hospital length-of-stay by as much as 16 days compared to BSC[4][5].
- **Quality of Life:** Long-term survivors experience comparable QALYs to the post-transplant population at large[4][1].

Economic Outcomes

Direct Drug Costs

- **Europe:** Average per-patient drug costs are €32,916-€40,344 for a typical course (adults), lower for children[2][6].
- **North America:** Estimated cost for a 21-day course in a 70-kg adult may reach $249,000; with possible maximum up to $710,000[7][8].
- **Cost Drivers:** Total drug cost is influenced by body weight, treatment duration, and wastage.

Hospital Resource Utilization

- **Hospitalization Costs Saved:** Defibrotide reduces the need for prolonged ICU care and additional interventions in survivors, producing average hospital stay savings of €16,644 per patient in some analyses[4][5].
- **Budget Impact:** The incremental annual cost for a transplant center was minor compared to the overall HSCT program budget (3% increase for adults; <1% for pediatrics)[1].

Cost-Effectiveness Results

Study/Setting	ICER/QALY (€ or $)	QALYs/LYs Gained	Comparator	Notes
Spain (Markov model)	€27,757 per QALY[4][5][9]	+1.214 QALYs, +1.348 LYs	BSC	Well below €30,000 threshold
Canada	$27,396 additional cost	+1.5 QALYs	BSC	ICER below local acceptability
US	$47,736 per QALY[1]	+2.24 QALYs, +3.74 LYs	BSC	88% probability under $100,000/QALY
Spain (Real-world)	€800 per life-day[6]	Median OS 56d	None	Bootstrap CI: €365–2,753 per day

Note: In all models, the ICER falls below conventional thresholds applied by payers in each region. Sensitivity analyses consistently confirm robustness against changes in hospitalization costs and drug price assumptions.

Graphical Representation

1. Incremental Cost-Effectiveness Ratio (ICER) of Defibrotide vs BSC

Comparator	Incremental Cost (€)	LYs Gained	QALYs Gained	ICER (€/QALY)
BSC	33,708	1.348	1.214	27,757

2. Survival Improvement with Defibrotide

Time Point	Survival with BSC	Survival with Defibrotide
100 days	~38%	~61%
1 year	<25% (est.)	~40-45%

DISCUSSION

- **Robust Cost-effectiveness:** All major analyses conclude defibrotide is a cost-effective therapy for severe SOS/VOD post-HSCT, with ICERs comfortably beneath standard willingness-to-pay thresholds[4][5][1][9].
- **Economic Justification:** While upfront costs are high, these are offset by survival gains, shortened resource utilization, and reductions in hospital/ICU stay.
- **Real-World Generalizability:** Economic conclusions are robust across multiple health systems including Europe, Canada, and the US.
- **Limitations:** Most economic models rely on historical controls for BSC, which may introduce bias and uncertainty. Real-world cost data variability should be considered.
- **Policy Implications:** The high price of defibrotide justifies restricting use to patients meeting strict diagnostic criteria for severe SOS with multi-organ dysfunction.

Limitations and Areas for Future Research

- Long-term utility data in survivors and broader quality-of-life assessment are needed.
- Additional prospective, multi-center cohort data would enhance the granularity and credibility of economic analyses.
- Comparative effectiveness vs. future novel agents should be continuously assessed

CONCLUSION

Defibrotide offers a clinically meaningful and economically justified option for patients with severe SOS/VOD post-HSCT, providing not only improved survival but also cost-effectiveness relative to supportive therapy alone. Targeted use in high-risk populations ensures maximum benefit and efficient healthcare expenditure

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