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Letter to *Blood*



TO THE EDITOR:

# Cost-effectiveness of liposomal cytarabine/daunorubicin in patients with newly diagnosed acute myeloid leukemia

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The liposomal formulation of cytarabine/daunorubicin (CPX-351) has been shown to improve overall survival (OS) in older (60-75 years of age) patients with newly diagnosed acute myeloid leukemia with myelodysplasia-related changes (AML-MRC) or therapy-related AML (t-AML) when compared with conventional cytarabine/daunorubicin (7 + 3).[1,2] Based on these results, CPX-351 was approved in the United States for the treatment of adult patients with newly diagnosed AML-MRC and t-AML. However, the health economic implications of this approval from a US payer perspective are not well-characterized.

We conducted a partitioned survival analysis based on data from the original phase 3 trial and post hoc analyses.[1-3] Similar to the original trial, newly diagnosed patients with AML at a median age of 68 years entered the model with active AML and received either CPX-351 or 7 + 3 induction and consolidation therapy. Frequency and setting (inpatient vs outpatient) of reinduction and consolidation therapy were used as outlined in the original study.[1] Parametric survival distributions were fitted using recreated patient-level data derived from the Kaplan-Meier curves and at-risk tables for event-free survival (EFS) and OS for both study arms.[4,5] EFS curves were derived from the original publication,[1] while OS curves were derived from a subsequent publication reporting a 5-year update (supplemental Figure 1 available on the *Blood* Web site).[2]

For the CPX-351 arm, we added the average sales price (ASP) for CPX-351 listed by the Centers for Medicare and Medicaid Services to the costs of induction and consolidation therapy in the 7 + 3 arm.[6,7] We assumed a total body surface area of 1.7 $m^2$ and accounted for drug wastage by rounding up to the next full single-use vial size available for each dose administered. Costs and practice patterns of salvage therapy, receipt of allo-HCT, supportive care, and incidence of complications were derived from the original trial or published literature (Table 1).[6,8-11] Costs were adjusted for inflation to 2020 US dollars using the personal consumption expenditure health index.[12]

Previously published utilities were used and measured in quality-adjusted life-years (QALYs).[13,14] Prior studies have demonstrated a higher utility among patients treated with CPX-351 compared with 7 + 3 while undergoing induction chemotherapy.[13] Therefore, we used different utilities during months 0 through 2 in the model, while keeping utilities constant across both arms at subsequent time points.

Costs and utilities were discounted by 3% annually.[15] We used a 10-year time-horizon to reflect the older patient population in the trial. Model outputs were used to calculate the incremental cost-effectiveness ratio (ICER) for CPX-351 over 7 + 3, with a conventional willingness-to-pay (WTP) threshold of $150 000/QALY. One-way sensitivity analyses were performed with utility values varied by a 10% range and all other variables across a 50% range. In probabilistic sensitivity analyses using 10 000 Monte Carlo simulations, β distributions were used to describe probabilities and utilities, whereas γ distributions were used for costs. Finally, we performed a sensitivity analysis evaluating the effect of the receipt of salvage therapy with novel targeted agents on the ICER (supplemental Materials). Original data can be requested from the corresponding author (e-mail: amer.zeidan@yale.edu).

Our parametric survival curves estimated a median EFS and OS of 3.1 and 9.7 months for CPX-351 and 1.4 and 6.4 months for 7 + 3, respectively, which was comparable to the results of the original trial.[1,2] CPX-351 and 7 + 3 were associated with lifetime costs of $415 258 and $256 415, respectively, for an incremental cost of $157 424 with CPX-351. Based on an incremental gain of 0.49 QALYs for CPX-351 compared with 7 + 3 (CPX-351: 1.11 QALYs vs 7 + 3: 0.62 QALYs), the ICER of the base-case model was $319 660/QALY.

In 1-way sensitivity analyses, our model was most sensitive to the probability of undergoing allo-HCT in either arm. Figure 1 shows the 10 variables with the greatest influence on the ICER. However, only a reduction in the ASP of CPX-351 by 79.6% (from $17 828 to $3635) would yield a reduction in the ICER below a WTP threshold of $150 000/QALY.

Probabilistic sensitivity analysis yielded a median ICER of $311 974 (95% credible interval: $231 660-$402 707) with 7 + 3 favored in 99.98% of 10 000 iterations at a WTP threshold of $150 000/QALY (supplemental Figure 2). Incorporating the potential use of targeted therapies (ie, gilteritinib, ivosidenib, and enasidenib) as salvage therapy for the subset of patients with *FLT3*, *IDH1*, or *IDH2* mutations had only a modest impact on the ICER (supplemental Materials).

Although CPX-351 has demonstrated superior efficacy and an acceptable safety profile in randomized phase 3 clinical trials

**Table 1. Costs and clinical variables included in the model**

| Model variable | CPX-351 | | 7 + 3 | | Ref. |
|---|---|---|---|---|---|
| | Base-case scenario | Range | Base-case scenario | Range | |
| **Treatment patterns** | | | | | |
| Probability of requiring reinduction | 0.31 | 0.16-0.47 | 0.34 | 0.17-0.51 | 3 |
| Probability of receiving cycle 1 of consolidation | 0.32 | 0.16-0.48 | 0.21 | 0.11-0.32 | 3 |
| Probability of receiving consolidation 1 as inpatient | 0.49 | 0.25-0.74 | 0.94 | 0.50-1.00 | 3 |
| Probability of receiving consolidation 1 as outpatient | 0.51 | 0.26-0.77 | 0.06 | 0.03-0.09 | 3 |
| Probability of receiving cycle 2 of consolidation | 0.15 | 0.08-0.22 | 0.08 | 0.04-0.12 | 3 |
| Probability of receiving consolidation 2 as inpatient | 0.39 | 0.20-0.59 | 1.0 | N/A | 3 |
| Probability of receiving consolidation 2 as outpatient | 0.61 | 0.31-0.92 | 0 | N/A | 3 |
| Probability to proceed to allo-HCT | 0.34 | 0.17-0.51 | 0.25 | 0.13-0.38 | 1 |
| Probability to receive salvage chemotherapy | 0.23 | 0.12-0.35 | 0.23 | 0.12-0.35 | 20 |
| Probability to receive LIT at time of relapse | 0.33 | 0.17-0.50 | 0.33 | 0.17-0.50 | 20 |
| Probability to proceed to hospice/BSC | 0.44 | 0.22-0.66 | 0.44 | 0.22-0.66 | 20 |
| **Costs** | | | | | |
| Cost of inpatient induction | | | | | 6,7 |
| Baseline AML induction cost for 1 cycle | $68 983 | $34 492-103 475 | $68 983 | $34 392-103 475 | |
| Baseline AML induction cost for 2 cycles | $134 484 | $67 242-201 726 | $134 484 | $67 242-201 726 | |
| CPX-351 drug cost-induction | $53 484 | $26 742-80 226 | N/A | | |
| CPX-351 drug cost-re-induction | $35 656 | $17 828-53 484 | N/A | | |
| Cost of inpatient consolidation per cycle | | | | | 6,7 |
| Baseline AML consolidation cost | $30 762 | $15 381-46 143 | $30 762 | $15 381-46 143 | |
| CPX-351 drug cost: consolidation | $35 656 | $17 828-53 484 | N/A | | |
| Cost of outpatient consolidation per cycle | | | | | 1,6,7 |
| Baseline outpatient consolidation cost | $6 189 | $3 095-9 284 | $6 189 | $3 095-9 284 | |
| CPX-351 drug cost per dose (2 doses) | $35 656 | $17 828-53 484 | N/A | | |
| Cost of salvage chemotherapy | $153 737 | $76 869-230 606 | $153 737 | $76 869-230 606 | 8 |
| Cost of LIT (cycle) | $10 522 | $5 261-15 783 | $10 522 | $5 261-15 783 | 9 |
| Number of other lower-intensity salvage therapy cycles | 6 | 3-9 cycles | 6 | 3-9 cycles | 9 |
| Cost of allo-HCT | $145 892 | $72 946-218 838 | $145 892 | $72 946-218 838 | 6 |
| Cost of office visit | $131 | $66-197 | $131 | $66-197 | 21 |
| Number of office visits (per mo) | 10.5 | 5-15 | 10.5 | 5-15 | 6 |
| Cost of hospice care (mo) | $1 129 | $565-1 694 | $1 129 | $565-1 694 | 11 |
| Cost of supportive care (mo) | $3 882 | $1 941-5 823 | $3 882 | $1 941-5 823 | 10 |
| Cost of terminal care | $8 890 | $4 445-13 335 | $8 890 | $4 445-13 335 | 6 |

BSC, best supportive care; ED, emergency department; LIT, lower-intensity therapy; N/A, not available.

**Table 1. (continued)**

| Model variable | CPX-351 | | 7 + 3 | | Ref. |
|---|---|---|---|---|---|
| | Base-case scenario | Range | Base-case scenario | Range | |
| Unplanned admission | | | | | 6 |
| Likelihood of unplanned admission | 0.4/mo | 0.2-0.6/mo | 0.4/mo | 0.2-0.6/mo | |
| Costs per episode | $17 220 | $8 610-25 830 | $17 220 | $8 610-25 830 | |
| ED visits | | | | | 6 |
| Likelihood of ED visit | 0.11/mo | 0.06-0.17/mo | 0.11/mo | 0.06-0.17/mo | |
| Costs per episode | $1 030 | $515-1 545 | $1 030 | $515-1 545 | |
| **Utilities** | | | | | |
| Utility during induction (months 0-2) | 0.44 | 0.40-0.48 | 0.40 | 0.36-0.44 | 13 |
| Utility during temporary remission (3-5 mo) | 0.66 | 0.60-0.72 | 0.66 | 0.60-0.72 | 13 |
| Utility during long-term remission (≥6 mo) | 0.82 | 0.74-0.90 | 0.82 | 0.74-0.90 | 14 |
| Utility during disease relapse | 0.53 | 0.48-0.58 | 0.53 | 0.48-0.53 | 14 |

BSC, best supportive care; ED, emergency department; LIT, lower-intensity therapy; N/A, not available.

compared with conventional 7 + 3, our model shows that CPX-351 is unlikely to be cost-effective for most older patients with AML-MRC or t-AML under current pricing.

Unlike continuous infusion of cytarabine during induction and consolidation with conventional 7 + 3, CPX-351 is administered as a 90-minute infusion. This allows outpatient administration and the potential for cost-saving opportunities related to avoidance of hospital admission. However, various aspects related to reimbursement structures need to be considered. Although drug acquisition costs are similar for outpatient and inpatient administration, Medicare uses a capitated reimbursement system based on diagnosis-related groups in the inpatient setting in contrast to individual itemized outpatient reimbursement. Thus, providers could be incentivized to shift the administration of expensive drugs such as CPX-351 to the outpatient setting because the actual drug acquisition costs may not be adequately captured in the diagnosis-related group. However, whether such a shift from inpatient to outpatient administration of CPX-351 is occurring and how it affects the cost-effectiveness of CPX-351 from both the Medicare and total health system perspective requires additional studies.

A major contributor to improved long-term outcomes with CPX-351 is the greater likelihood of proceeding to allo-HCT.[1,16] Because allo-HCT offers the highest likelihood of cure for many patients with AML, a higher proportion of patients proceeding to allo-HCT and achieving durable remission could have a positive effect on the cost-effectiveness of CPX-351. Although our model used an older patient population similar to the original trial,[1] CPX-351 is approved for patients ≥18 years old in the United States. However, whether the OS benefit of CPX-351

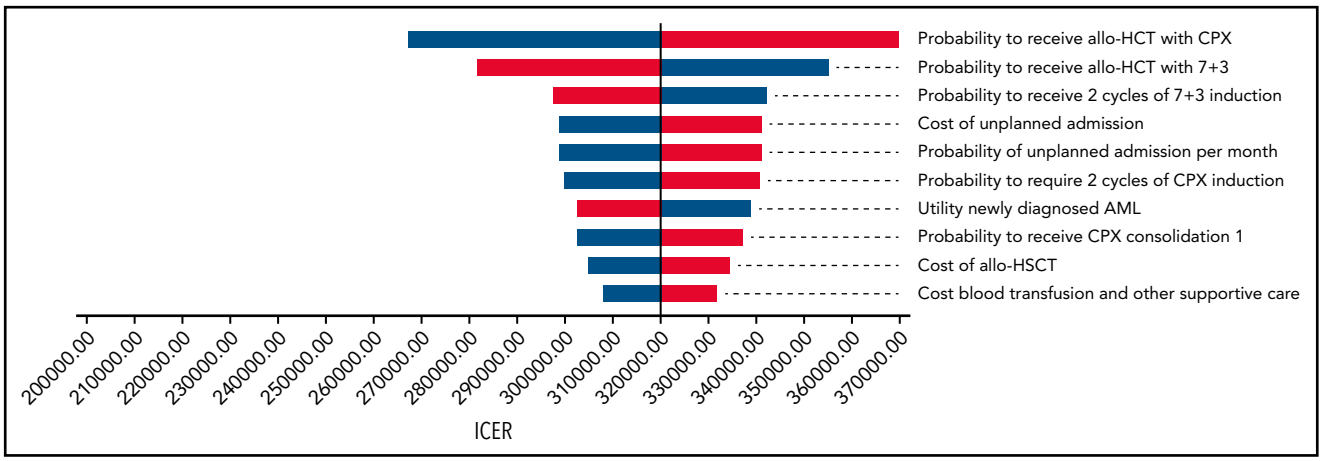


**Figure 1. One-way sensitivity analysis of the 10 most influential variables on the ICER.** Figure 1 shows a tornado diagram of the 10 most influential model variables and their influence on the ICER. Variables were varied by 50% for costs and probabilities and by 10% for utilities as outlined in Table 1. Blue bars represent the lower value in the range, whereas red bars represent the higher value. Our model was most sensitive to the proportion of patients proceeding to allo-HCT. However, none of the variables included in our model was able to lower the ICER below the WTP threshold of $150 000/QALY gained.

over 7 + 3 also extends to younger patients with AML (<60 years) is unclear.[17,18] Because expanding use of CPX-351 to younger AML patients (<60 years) may result in a higher percentage of patients proceeding to allo-HCT than in the original trial, the QALYs gained could also be greater, resulting in a lower ICER. However, in our sensitivity analyses, which varied the probability of undergoing allo-HCT by 50%, the ICER for CPX-351 remained above the WTP threshold.

The prices of novel drugs for AML in the United States are very expensive, and ICERs as high as $486 000/QALY for oral azacitidine have been reported.[19] Although it could be argued that the conventional WTP threshold of $150 000/QALY should be reconsidered in some settings, it is important with the continued approval of expensive novel drugs to consider their health economic implications.

Potential limitations of our study include differences between clinical trials and real-world practice in terms of patient characteristics and health care utilization. Also, the number of patients with specific mutations other than *FLT3* that would allow for targeted salvage therapies (eg, IDH1/2 inhibitors) was not reported in the original trial, but could influence the cost of salvage therapies. However, a sensitivity analysis incorporating the potential use of targeted therapies had only a modest impact on the ICER. Finally, our model is from a US payer perspective, limiting its generalizability to other countries with varying health care expenses and practice patterns.

In summary, we conducted a partitioned survival analysis to evaluate the cost-effectiveness of CPX-351 compared with 7 + 3 in newly diagnosed, older patients with AML-MRC or t-AML. Our model yielded an ICER of $319 660/QALY for CPX-351, which is substantially above the conventional WTP threshold of $150 000/QALY. Neither higher rates of allo-HCT nor outpatient consolidation with CPX-351 led to gains in clinical utility or cost reductions substantial enough to make CPX-351 cost-effective. A reduction in the ASP of CPX-351 by 79.6% would be necessary to lower the ICER below $150 000/QALY.

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## Authorship

Contribution: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; all authors were responsible for conception and design, acquired, analyzed, interpreted the data, and drafted the manuscript; J.P.B., K.K.P., and G.G. performed statistical analysis; K.K.P., S.F.H., and A.M.Z. obtained funding; and A.M.Z. and S.F.H. supervised the study.

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## Footnotes

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### REFERENCES

1. Lancet JE, Uy GL, Cortes JE, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. *J Clin Oncol*. 2018;36(26):2684-2692.

2. Lancet JE, Uy GL, Newell LF, et al. CPX-351 versus 7 + 3 cytarabine and daunorubicin chemotherapy in older adults with newly diagnosed high-risk or secondary acute myeloid leukaemia: 5-year results of a randomised, open-label, multicentre, phase 3 trial. *Lancet Haematol*. 2021;8(7):e481-e491.

3. Villa KF, Ryan RJ, Chiarella M, Louie AC. Healthcare resource utilization in a phase 3 study of CPX-351 in patients with newly diagnosed high-risk/secondary acute myeloid leukemia. *J Med Econ*. 2020;23(7):714-720.

4. Patel KK, Zeidan AM, Shallis RM, Prebet T, Podoltsev N, Huntington SF. Cost-effectiveness of azacitidine and venetoclax in unfit patients with previously untreated acute myeloid leukemia. *Blood Adv*. 2021;5(4):994-1002.

5. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol*. 2012;12(1):9.

6. Stein EM, Bonifacio G, Latremouille-Viau D, et al. Treatment patterns, healthcare resource utilization, and costs in patients with acute myeloid leukemia in commercially insured and Medicare populations. *J Med Econ*. 2018;21(6):556-563.

7. Centers for Medicare & Medicaid Services. ASP Drug Pricing Files October 2021 Update. https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/2021-asp-drug-pricing-files. Accessed 6 October 2021.

8. Irish W, Ryan M, Gache L, Gunnarsson C, Bell T, Shapiro M. Acute myeloid leukemia: a retrospective claims analysis of resource utilization and expenditures for newly diagnosed patients from first-line induction to remission and relapse. *Curr Med Res Opin*. 2017;33(3):519-527.

9. Zeidan AM, Mahmoud D, Kucmin-Bemelmans IT, et al. Economic burden associated with acute myeloid leukemia treatment. *Expert Rev Hematol*. 2016;9(1):79-89.

10. Bell JA, Galaznik A, Farrelly E, et al. Economic burden of elderly patients with acute myeloid leukemia treated in routine clinical care in the United States. *Leuk Res*. 2018;71:27-33.

11. Duncan I, Ahmed T, Dove H, Maxwell TL. Medicare cost at end of life. *Am J Hosp Palliat Care*. 2019;36(8):705-710.

12. Bureau of Economic Analysis US Department of Commerce. Table 2.5.4. Price Indexes for Personal Consumption Expenditures by Function. https://apps.bea.gov/iTable/iTable.cfm?reqid=19&step=2#reqid=19&step=2&isuri=1&1921=survey. Accessed 10 March 2021.

13. Matza LS, Deger KA, Howell TA, et al. Health state utilities associated with treatment options for acute myeloid leukemia (AML). *J Med Econ*. 2019;22(6):567-576.

14. Forsythe A, Brandt PS, Dolph M, Patel S, Rabe APJ, Tremblay G. Systematic review of health state utility values for acute myeloid leukemia. *Clinicoecon Outcomes Res*. 2018;10:83-92.

15. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *JAMA*. 2016;316(10):1093-1103.

16. Guolo F, Fianchi L, Minetto P, et al. CPX-351 treatment in secondary acute myeloblastic leukemia is effective and improves the feasibility of allogeneic stem cell transplantation: results of the Italian compassionate use program. *Blood Cancer J*. 2020;10(10):96.

17. Chiche E, Rahmé R, Bertoli S, et al. Real-life experience with CPX-351 and impact on the outcome of high-risk AML patients: a multicentric French cohort. *Blood Adv*. 2021;5(1):176-184.

18. Lee D, Asghari HH, Deutsch YE, et al. CPX-351 as induction chemotherapy yields similar responses and survival outcomes in younger patients (<60 years old) compared to older patients (≥60 years old) with acute myeloid leukemia. *Blood*. 2019;134(suppl 1):3894.

19. Bewersdorf JP, Patel KK, Huntington SF, Zeidan AM. Cost-effectiveness analysis of oral azacitidine maintenance therapy in acute myeloid leukemia. *Blood Adv*. 2021;5(22):4686-4690.

20. Brandwein JM, Saini L, Geddes MN, et al. Outcomes of patients with relapsed or refractory acute myeloid leukemia: a population-based real-world study. *Am J Blood Res*. 2020;10(4):124-133.

21. Centers for Medicare & Medicaid Services. Physician fee schedule. https://www.cms.gov/medicare/physician-fee-schedule/search?Y=0&T=0&HT=0&CT=0&H1=96413&M=5. Accessed 27 June 2021.

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