ORIGINAL RESEARCH

Budget Impact Analysis of Using Daunorubicin-Cytarabine Liposome in Patients with Newly Diagnosed Therapy-Related AML or AML and Myelodysplasia-Related Changes

Ivar S. Jensen, MBA; Elizabeth Wu, MPH; Naomi C. Sacks, PhD; Philip L. Cyr, MPH; Karen C. Chung, PharmD, MS

BACKGROUND: Current national estimates for acute myelogenous leukemia (AML) indicate this disease accounts for 1.1% of new cancer diagnoses and 1.8% of cancer deaths in the United States. The 5-year overall survival rate for patients with AML was 27.4% between 2008 and 2014. The standard induction for patients with AML includes cytarabine, infused for 7 days, with 3 once-daily injections of an anthracycline, such as daunorubicin, known as the 7+3 regimen. Daunorubicin plus cytarabine liposomal encapsulation for injection was approved in the United States in 2017 for adults with newly diagnosed therapy-related AML (tAML) or AML with myelodysplasia-related changes (AML-MRC).

OBJECTIVE: To estimate the annual budget impact of introducing daunorubicin-cytarabine liposome as induction treatment for patients with tAML or AML-MRC in the United States over a 3-year period.

METHODS: The model consisted of a simple decision analytic framework for a 1- to 3-year period. We used an incidence-based approach to estimate the annual number of patients newly diagnosed with tAML or AML-MRC in a hypothetical 1-million-member plan. Patients were allocated to 2 groups based on when daunorubicin-cytarabine liposome became available, with the base-case group allocated to the 7+3 regimen, and another group allocated to daunorubicin-cytarabine liposome treatment. The incidence of AML was estimated as 4.3 per 100,000 people. Efficacy measures included the proportion of complete responders, proportion of patients who had undergone transplantation, and survival at 180 and 365 days. Inpatient drug and hospitalization costs were based on diagnosis-related group rates, and outpatient drug costs on wholesale acquisition costs.

RESULTS: Based on this hypothetical 1-million-member health plan, 15.1 members would receive intensive induction for newly diagnosed tAML or AML-MRC annually. Increasing the use of daunorubicin-cytarabine liposome (assumption of year 1, 20%; year 2, 50%; year 3, 80%) resulted in a 3-year incremental cumulative budget impact of $72,041 (1.7% increase for patients with tAML or AML-MRC), with a per-member per-month cost of $0.0032 at year 3. Over a 3-year period, the use of daunorubicin-cytarabine liposome would result in an estimated increase in the number of patients with a complete response to therapy by 2.72 (23.1%), which would lead to an incremental cost decrease of $179,956 per responding patient compared with the use of the 7+3 regimen in the base-case group.

CONCLUSIONS: Based on these results, induction treatment with daunorubicin-cytarabine liposome for patients with tAML or AML-MRC instead of the 7+3 regimen may have a limited economic impact on the budget of commercial health plans and may result in cost offsets, particularly in patients who respond to therapy.

Am Health Drug Benefits.
2018;11(7):380-386
www.AHDBonline.com

Manuscript received June 22, 2018
Accepted in final form September 14, 2018

Disclosures are at end of text
Supplemental materials online

KEY WORDS: acute myelogenous leukemia, AML with myelodysplasia-related changes, budget impact, daunorubicin-cytarabine liposome, incremental cost, 7+3 regimen, tAML, therapy-related AML

Mr Jensen is Director, Evidence Strategy & Generation, Precision Xtract, Boston, MA; Ms Wu is Health Economist, Evidence Strategy & Generation, Precision Xtract; Dr Sacks is Director, Evidence Strategy & Generation, Precision Xtract, and Adjunct Professor, Tufts University School of Medicine, Boston; Mr Cyr is Vice President, Evidence Strategy & Generation, Precision Xtract, and Research Faculty, University of North Carolina, Charlotte; Dr Chung was Director, Health Economics & Outcomes Research, Jazz Pharmaceuticals, Palo Alto, CA, during the study.

KEY POINTS

- Induction treatment for patients with AML includes cytarabine, infused for 7 days, and 3 once-daily injections of an anthracycline (eg, daunorubicin), a regimen known as "7+3."
- A new therapy of daunorubicin plus cytarabine liposome for injection was approved in the United States in 2017 for adults with newly diagnosed tAML or AML-MRC.
- This economic analysis compared the annual impact of using daunorubicin-cytarabine liposome as induction therapy in this patient population in a hypothetical 1-million-member plan.
- Increasing the use of daunorubicin-cytarabine liposome resulted in a 3-year incremental cumulative increase of $72,041 and an incremental per-member per-month increase of $0.0032 at year 3.
- Adoption of induction with daunorubicin-cytarabine liposome resulted in a 3-year incremental cost decrease of $179,956 per responder versus the 7+3 regimen.
- Increases in the costs of outpatient drugs ($124,073), administration ($5386), and AEs ($46,603) with this new drug were partially offset by inpatient savings of $104,021.

In 2018, acute myelogenous leukemia (AML) is estimated to account for 1.1% of new cancer diagnoses and 1.8% of cancer deaths in the United States.[1] Between 2008 and 2014, the overall 5-year survival rate for patients with AML was 27.4%.[1] AML primarily affects older patients (median age at diagnosis, 68 years),[1] and outcomes are poor among patients aged >65 years,[2-4] with an estimated 5-year survival rate of 7.1% in this population.[1] Allogeneic hematopoietic stem-cell transplant (HSCT) may lead to durable responses in AML; however, achieving a complete response to chemotherapy is often a prerequisite for HSCT.

In the United States, the standard induction treatment for patients with AML is cytarabine, infused continuously for 7 days, with 3 once-daily infusions of an anthracycline, such as daunorubicin.[5] This regimen is known as "7+3" and has remained a standard-of-care therapy for decades. Conventional AML induction chemotherapy is typically administered in a hospital setting because of the prolonged infusion, and patients often remain in the hospital after induction to facilitate the monitoring of treatment-related toxicities.[6]

In a recent real-world analysis of medical claims from multiple US Truven Health MarketScan databases between 2009 and 2015, approximately $153,000 of the almost $182,000 mean cost per newly diagnosed patient with AML was attributed to inpatient expenses.[6] Based on this analysis, a disproportionate share of the cost burden associated with AML management comes from hospitalization.[6] In August 2017, the US Food and Drug Administration approved daunorubicin and cytarabine liposome for injection for the treatment of adults with newly diagnosed, therapy-related AML (tAML) or AML with myelodysplasia-related changes (AML-MRC).[7] This drug is a liposomal encapsulation of cytarabine and daunorubicin at a synergistic molar ratio.[8-12]

When administered as free drugs, as with the conventional 7+3 regimen, cytarabine and daunorubicin have different pharmacokinetic profiles (eg, terminal half-lives of 1-3 hours and 18.5 hours, respectively); consequently, the achievement of a particular synergistic molar ratio is only transiently achieved and can never be maintained. In preclinical studies, a 5:1 molar ratio of cytarabine:daunorubicin had synergistic cytotoxicity in leukemic cells.[9] In xenograft models, daunorubicin-cytarabine liposome demonstrated greater tumor-cell cytotoxicity than nonliposomal cytarabine and daunorubicin administered at a 5:1 ratio.[10] Furthermore, the uptake of daunorubicin-cytarabine liposomes occurs in leukemic cells to a greater extent than in normal cells in the bone marrow,[10,11] which can increase tumor-cell exposure while minimizing off-target effects.

In a first-in-human clinical trial, daunorubicin-cytarabine liposome administration maintained exposure to a synergistic drug ratio for >24 hours, and drug exposure was maintained for approximately 7 days.[12] In a randomized, phase 3 clinical trial comparing daunorubicin-cytarabine liposome and the 7+3 regimen in older patients with newly diagnosed tAML or AML-MRC, daunorubicin-cytarabine liposome significantly improved overall survival and remission rates.[13] In addition, because the site of administration (inpatient vs outpatient) was left to the physicians' discretion, approximately 50% of patients received daunorubicin-cytarabine liposome consolidation in an outpatient setting.[14]

Daunorubicin-cytarabine liposome is recommended by the National Comprehensive Cancer Network (NCCN) clinical guidelines for the treatment of patients with AML (level 1 and level 2b recommendations for patients aged >60 years and <60 years, respectively).[5]

Given the differences in efficacy, dosing, and administration between daunorubicin-cytarabine liposome and the 7+3 regimen, the goal of the study was to estimate the annual budget impact of introducing daunorubicin-cytarabine liposome to the US healthcare market over a 3-year period.

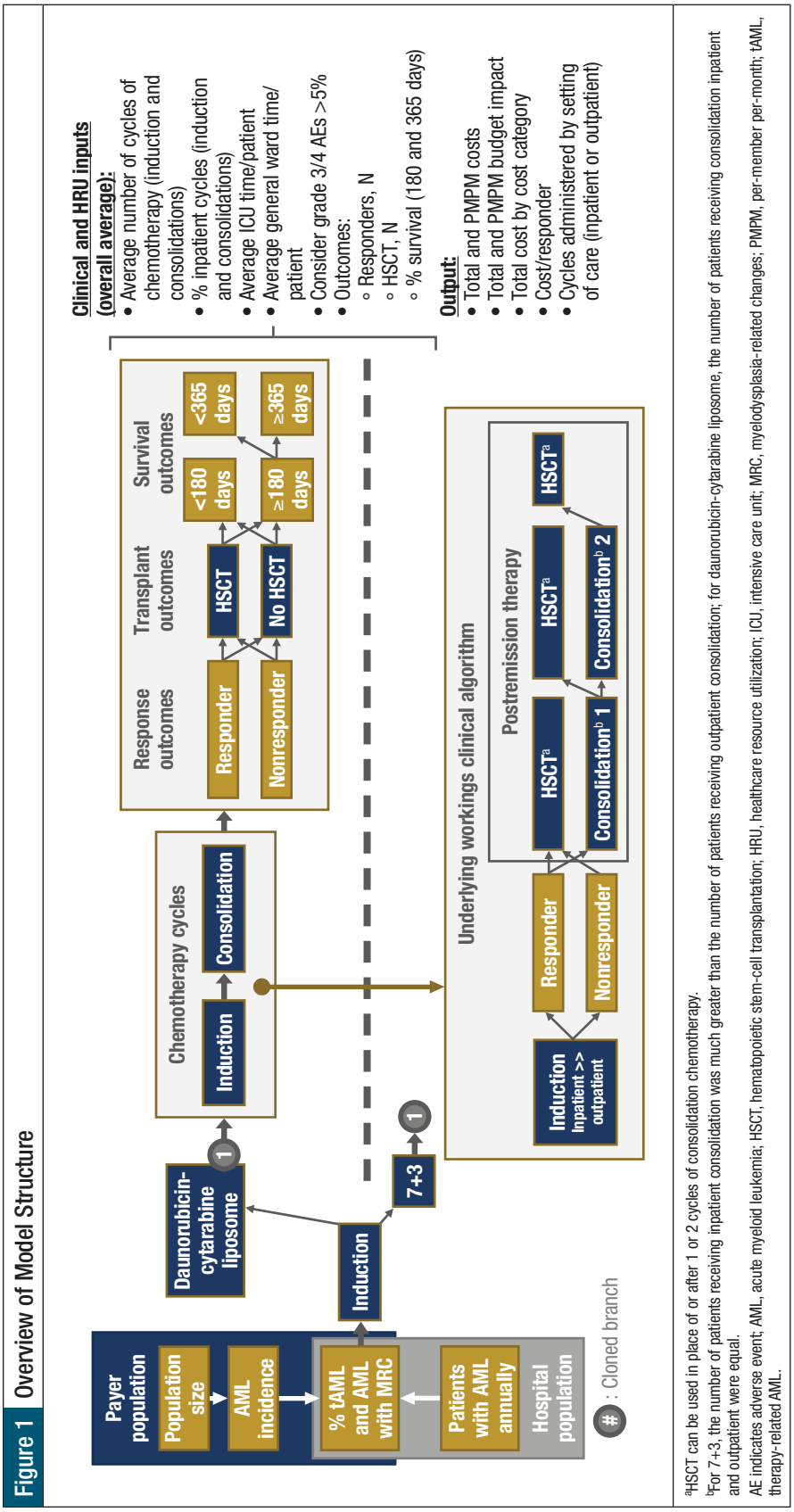


Figure 1 Overview of Model Structure

[a]HSCT can be used in place of or after 1 or 2 cycles of consolidation chemotherapy.
[b]For 7+3, the number of patients receiving inpatient consolidation was much greater than the number of patients receiving outpatient consolidation; for daunorubicin-cytarabine liposome, the number of patients receiving consolidation inpatient and outpatient were equal.
AE indicates adverse event; AML, acute myeloid leukemia; HSCT, hematopoietic stem-cell transplantation; HRU, healthcare resource utilization; ICU, intensive care unit; MRC, myelodysplasia-related changes; PMPM, per-member per-month; tAML, therapy-related AML.

Methods

The model structure consisted of a simple decision analytic framework for a 1- to 3-year period (**Figure 1**). The algorithm was developed based on the NCCN clinical practice guidelines for AML[5] and was validated by an oncologist. We used an incidence-based approach to estimate the annual number of patients newly diagnosed with tAML or AML-MRC in the hypothetical 1-million-member plan.

The patients were allocated to treatment based on when daunorubicin-cytarabine liposome became available; before its availability, the base-case group included only the 7+3 regimen, and the group after its availability included daunorubicin-cytarabine liposome as a treatment option.

Patients who were allocated to the 7+3 regimen received an initial induction course of cytarabine 100 mg/m^2 daily by 7-day continuous infusion plus daunorubicin 60 mg/m^2 on days 1 to 3; these patients might also have received a second induction course and/or postremission consolidation courses consisting of cytarabine 100 mg/m^2 daily by 5-day continuous infusion plus daunorubicin 60 mg/m^2 on days 1 and 2, known as the 5+2 regimen.

Patients allocated to daunorubicin-cytarabine liposome received 1 or 2 courses of 90-minute infusions of a dose corresponding to cytarabine 100 mg/m^2 plus daunorubicin 44 mg/m^2 on days 1, 3, and 5 for first induction and on days 1 and 3 for second induction; the postremission consolidation courses consisted of 90-minute infusions of a dose corresponding to cytarabine 65 mg/m^2 plus daunorubicin 29 mg/m^2 on days 1 and 3.

The eligible patients were modeled over a 3-year period, starting from induction with the 7+3 regimen or with daunorubicin-cytarabine liposome therapy. The model compared the scenarios before and after the availability of daunorubicin-cytarabine liposome.

The incidence of AML in the United States was estimated to be 4.3 per 100,000 people, based on the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program.[1] The proportion of patients with AML who have

tAML or AML-MRC was estimated to be 36%, based on SEER data and on data presented at the European Hematology Association meeting in June 2017.[1,15] Based on a retrospective claims analysis of patients with AML that used data from multiple Truven Health MarketScan databases, 32.4%, 3.4%, and 64.3% of patients were estimated to be covered under Medicare, Medicaid, and commercial insurance, respectively.[6] Our model assumed a hypothetical health plan population of 1 million covered patients.[6]

Clinical Inputs

The efficacy used in our model included the proportion of complete responders, proportion of patients who received HSCT, and survival at 180 and 365 days (**Appendix Table S1** at **www.AHDBonline.com**). The values for these outcomes were based on data from the pivotal phase 3, randomized, controlled clinical trial comparing daunorubicin-cytarabine liposome with the 7+3 regimen.[13] The model also considered nonhematologic adverse event (AE) data from that study, which are detailed in the prescribing information of daunorubicin-cytarabine liposome.[7,16] Specifically, all grade ≥3 nonhematologic AEs that occurred in ≥5% of patients were included in the model (**Appendix Table S2**).

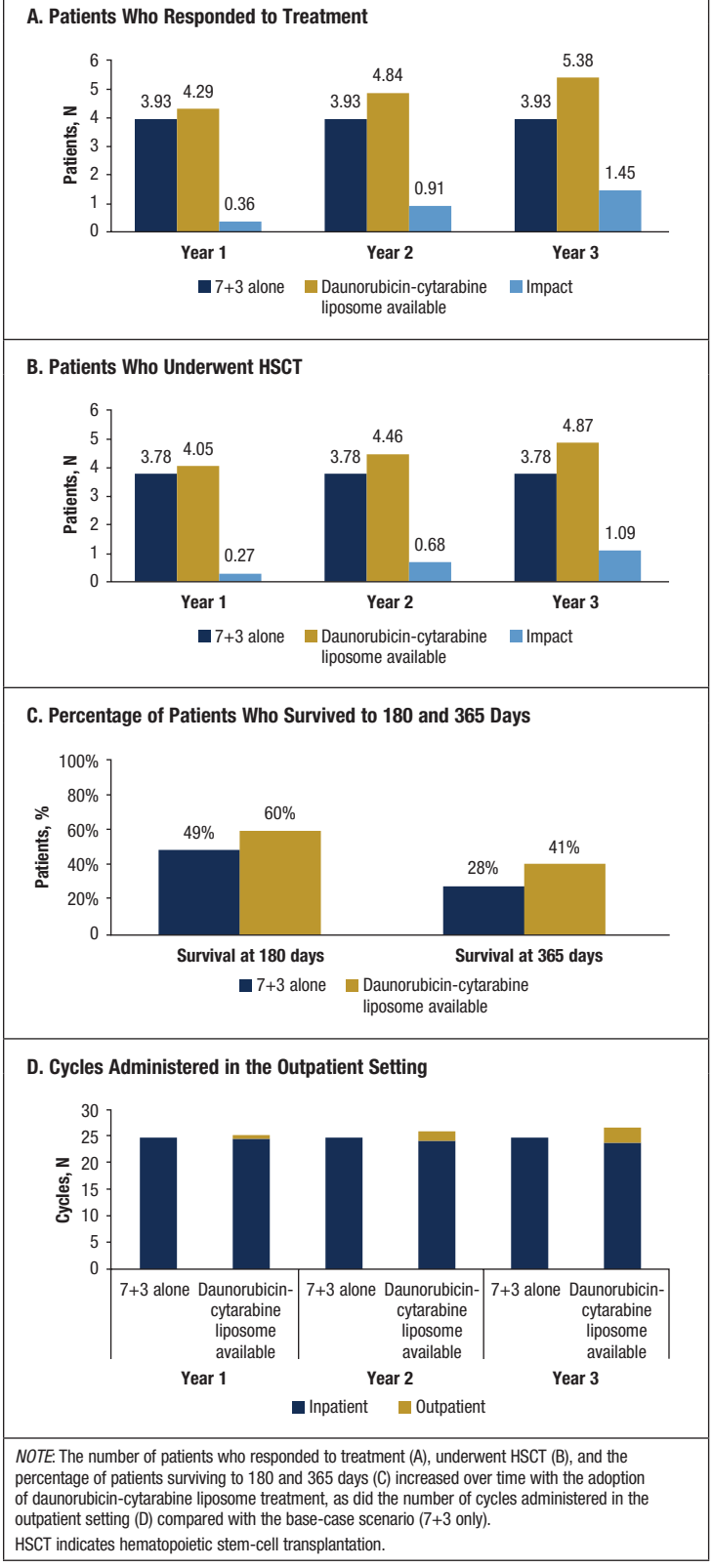
Whereas the 7+3 induction regimen and the 5+2 consolidation regimen include 7-day and 5-day continuous infusion of chemotherapy, respectively, daunorubicin-cytarabine liposome is administered as 90-minute infusions on days 1, 3, and 5 (ie, first induction only) and thus can be administered in the outpatient setting for some patients. Although the majority of patients received daunorubicin-cytarabine liposome induction on an inpatient basis in the phase 3 clinical trial, approximately 50% of the consolidation treatments with daunorubicin-cytarabine liposome occurred in an outpatient setting.[14]

Therefore, our model assumed that 100% of daunorubicin-cytarabine liposome induction therapy would be administered in the inpatient setting and 50% of consolidation treatments would be administered in the outpatient setting. By contrast, all induction and consolidation treatments in the 7+3 treatment arm were assumed to be administered in the inpatient setting because of the continuous, multiple-day infusion.

Cost Data

Inpatient drug costs and inpatient hospitalization costs to the health plan were assumed to align with diagnosis-related group rates (**Appendix Table S3**), which were sourced from the 2013 Centers for Medicare & Medicaid Services (CMS) Limited Data Set; CMS rates were used as a proxy for commercial costs, because there are no standard costs across commercial payers.

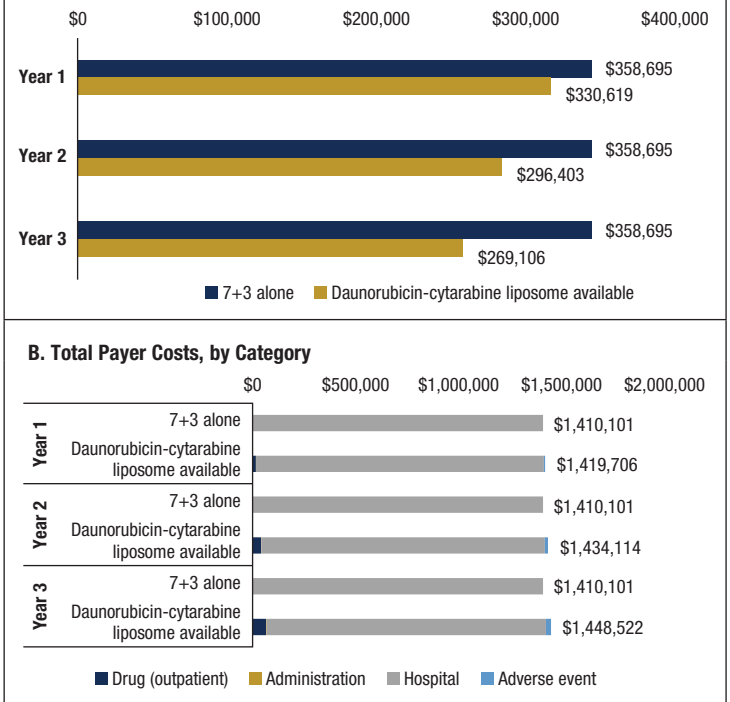
Figure 2 Effect of Adoption of Daunorubicin-Cytarabine Liposome on Clinical End Points



NOTE: The number of patients who responded to treatment (A), underwent HSCT (B), and the percentage of patients surviving to 180 and 365 days (C) increased over time with the adoption of daunorubicin-cytarabine liposome treatment, as did the number of cycles administered in the outpatient setting (D) compared with the base-case scenario (7+3 only).

HSCT indicates hematopoietic stem-cell transplantation.

Figure 3 Budget Impact of Adoption of Daunorubicin-Cytarabine Liposome



NOTE: Model estimates of the costs per responder (A) and total payer costs by category (B) of adopting daunorubicin-cytarabine liposome versus the base-case scenario (7+3 only) are shown.

Table Summary Results of Patients with tAML or AML-MRC

Results summary	Year 1	Year 2	Year 3	Cumulative
Size of population (covered lives), N	1 million	1 million	1 million	
Total eligible patients starting treatment, N	15.1	15.1	15.1	45.3
Patients starting treatment with daunorubicin-cytarabine liposome, N	3.02	7.55	12.08	22.65
Incremental cost of adding daunorubicin-cytarabine liposome, $	9605	24,014	38,422	72,041
Incremental cost per responder, $	–28,075	–62,292	–89,589	–179,956
Incremental cost PMPM, $	0.0008	0.0020	0.0032	0.0060
Percentage budget impact of adding daunorubicin-cytarabine liposome, %	0.68	1.7	2.7	1.7
Incremental costs				
Total outpatient drug costs, $	16,543	41,358	66,172	124,073
Total administration costs, $	718	1795	2873	5386
Total inpatient costs, $	–13,869	–34,674	–55,478	–104,021
Total AE costs, $	6214	15,534	24,855	46,603
Total costs, $	9605	24,014	38,422	72,041

AE indicates adverse event; AML-MRC, acute myeloid leukemia with myelodysplasia-related changes; PMPM, per member per month; tAML, therapy-related acute myeloid leukemia.

We calculated the outpatient drug costs using wholesale acquisition costs (**Appendix Table S4**), the number of chemotherapy cycles per patient (**Appendix Table S5**), average body surface area, and the drug costs per cycle (**Appendix Table S6**).

For the 7+3 regimen, the wholesale acquisition cost was derived from Truven Health Analytics' RED BOOK. The outpatient administration costs (**Appendix Table S7**) were derived from the 2017 CMS Physician Fee Schedule by *Current Procedural Terminology* code for Medicare-covered patients and InGauge Healthcare Solutions for commercially covered patients. AE-related costs (**Appendix Table S8**) were sourced from the 2017 Healthcare Cost and Utilization Project using *International Classification of Diseases, Ninth Revision, Clinical Modification* codes.

Results

Our model estimated the impact of using daunorubicin-cytarabine liposome for a hypothetical commercial health plan covering 1 million members. In this patient population, we estimated that 15.1 patients would receive intensive induction treatment for tAML or AML-MRC annually. Overall, the introduction of daunorubicin-cytarabine liposome increased the number of patients with positive outcomes compared with the base-case, namely, those who received the 7+3 regimen (**Figure 2**).

Over a hypothetical 3-year period, the adoption of daunorubicin-cytarabine liposome increased the incremental number of responding patients by 2.72 (a 23.1% increase) and the number of patients undergoing HSCT by 2.04 (an 18% increase; Figures 2A and 2B). The addition of this new drug also increased the 180- and 365-day survival rates by 11% and 13%, respectively (Figure 2C), and the cumulative number of outpatient chemotherapy cycles by 5.34 cycles (Figure 2D).

Budget Impact Analysis

Our model also estimated the budget impact of daunorubicin-cytarabine liposome availability in this hypothetical patient population (**Figure 3**). The estimated cumulative 3-year cost for the base-case was $4,230,303 (ie, $1,410,101 annually).

By contrast, the estimated cumulative 3-year cost after the introduction of daunorubicin-cytarabine liposome was $4,302,343 (ie, $1,419,706, $1,434,114, and $1,448,522 in years 1, 2, and 3, respectively), which resulted in a 3-year incremental cumulative impact of $72,041. This represents a 1.7% increase in the health plan's 3-year budget for patients with tAML or AML-MRC (**Table**).

These calculations result in an incremental per-member per-month (PMPM) cost of $0.0032 at year 3 after the introduction of daunorubicin-cytarabine liposome

(Table 1). When measuring the cost per responder, the adoption of daunorubicin-cytarabine liposome results in a 3-year incremental decrease of $179,956 per responder compared with the base-case of the 7+3 regimen, which reflects the increased effectiveness of daunorubicin-cytarabine liposome (Table, Figure 3A).

Furthermore, the increases in the incremental costs of outpatient drugs ($124,073), administration ($5386), and AEs ($46,603) with the introduction of daunorubicin-cytarabine liposome were partially offset by a savings of $104,021 in inpatient costs (Table, Figure 3B).

Sensitivity Analysis

Several scenarios were analyzed to test the sensitivity of the model. If 100% of the daunorubicin-cytarabine liposome uptake in year 1 is assumed, which represents the maximum economic impact, an estimated incremental overall PMPM would be an increase of $0.004, and a $104,913 reduction in the cost per responder compared with the base-case scenario (**Appendix Figure S1**).

When patients with a complete response and incomplete neutrophil or platelet recovery were considered responders, the estimated incremental PMPM cost of introducing daunorubicin-cytarabine liposome was $0.0032 by year 3 (**Appendix Figure S2**). When an exclusively commercially insured population was assumed, the estimated incremental PMPM cost of introducing daunorubicin-cytarabine liposome was $0.0025 by year 3 (**Appendix Figure S3**); for a population exclusively funded by Medicare, the estimated incremental PMPM cost was $0.0045 by year 3 (**Appendix Figure S4**).

Finally, when 100% outpatient consolidation was assumed for daunorubicin-cytarabine liposome, a greater reduction in cost per responder was seen, in part because of an offset in hospitalization costs (**Appendix Figure S5**). Taken together, these results demonstrated the robustness of the model.

Discussion

Daunorubicin-cytarabine liposome has demonstrated significant survival benefit compared with the conventional 7+3 regimen in a randomized, controlled phase 3 study in older adults with newly diagnosed tAML or AML-MRC.[13]

Our budget impact model accounted for the costs associated with drug acquisition and administration, site of care, and the management of AEs. The model calculated a greater number of positive responses to treatment with daunorubicin-cytarabine liposome than with the base-case, including a higher proportion of responders, a greater number of patients receiving HSCT, and prolonged 180- and 360-day survival, based on data from the phase 3 study.

The model calculated a $0.0032 increase at year 3 after the introduction of daunorubicin-cytarabine liposome, which was driven primarily by increased drug costs. However, our model also identified offsets to hospitalization costs, and the incremental increase in PMPM costs was negligible. Sensitivity analyses were used to evaluate the robustness of the model. Several hypothetical scenarios were tested by customizing various parameters, such as daunorubicin-cytarabine liposome site of consolidation administration. In these scenarios, the impact of the adoption of daunorubicin-cytarabine liposome on the increase in PMPM costs was minimal, ranging from $0.0025 to $0.0045 by year 3.

Although several factors might have contributed to the estimated decrease in hospitalization costs, the reduced time in the inpatient setting that resulted from the administration of outpatient consolidation had the most substantial impact. Indeed, in the sensitivity analysis that assumed 100% administration of daunorubicin-cytarabine liposome in the outpatient setting, the overall cost of adoption of daunorubicin-cytarabine liposome over 3 years was lower than with the base-case of the 7+3 regimen, despite increased drug costs.

In the pivotal phase 3 clinical trial, outpatient consolidation with the new drug exceeded 50% when investigators were allowed to choose the site of administration.[14] As physicians gain experience and comfort with prescribing this drug, the proportion of patients receiving outpatient consolidation may increase, although it is unlikely to reach the maximal effect posited in the sensitivity scenario.

In addition, in the phase 3 study, a significantly higher overall response rate was achieved with the daunorubicin-cytarabine liposome regimen (approximately 48%) compared with the conventional 7+3 regimen (approximately 33%; 2-sided $P = .016$).[13] The increased efficacy of daunorubicin-cytarabine liposome compared with the 7+3 regimen is reflected in an attenuated cost per responder with its adoption. Furthermore, in the base-case model, responders were only patients with a complete response. In a sensitivity scenario that defined response more broadly to include patients with a complete response or a complete response with incomplete recovery of platelets and neutrophils, an even greater decrease in the cost per responder was observed ($213,748 with daunorubicin-cytarabine liposome vs $280,062 with the 7+3 regimen in year 3).

Limitations

This study should be considered with its limitations. Claims databases inherently have limitations, including potential underreporting of conditions, coding

errors, and lack of detailed clinical information (eg, laboratory values).

The limitations to the model include restriction to the time a patient is expected to receive treatment, with posttreatment costs for maintenance or additional lines of therapy that were not captured in the model. Thus, factors such as relapse-free survival and treatment costs for patients with relapsed disease were not incorporated into our model.

In addition, our model did not account for potential regimen changes during a patient's course of treatment or the use of less-common alternate chemotherapy regimens, which may occur in a real-world setting.

Finally, the model is based on clinical trial data and was built on a simplified scenario that may not be generalizable across all settings and may not reflect real-world practice.

These limitations may influence the reliability and validity of the study's findings.

Conclusion

Because the treatment of patients with AML is associated with substantial healthcare resource utilization and cost, it is important for healthcare payers to quantify the potential budget impact of new therapies. Based on the results of this budget impact analysis, the adoption of daunorubicin-cytarabine liposome for the treatment of patients with newly diagnosed tAML or AML-MRC may have a limited effect on commercial health plans' budgets and may result in cost offsets, particularly for patients whose disease responds to therapy.

Acknowledgments

The authors thank Arthur C. Louie, MD, for his expert advice and insight with validating our decision analytic framework, and Kimberly Brooks, PhD, CMPP, for her assistance in preparing this manuscript.

Funding Source

This study was funded by Jazz Pharmaceuticals, Inc.

Author Disclosure Statement

Mr Jensen, Ms Wu, Dr Sacks, and Mr Cyr are employees of Precision Xtract, which received funding for this study; Dr Chung was an employee of Jazz Pharmaceuticals and Gilead during this study, is currently an employee of Celgene, and holds stock in Baxter, Bayer, Celgene, Gilead, Jazz Pharmaceuticals, and Shire.

References

1. National Cancer Institute. SEER cancer stat facts: leukemia – acute myeloid leukemia (AML). http://seer.cancer.gov/statfacts/html/amyl.html. Accessed August 21, 2018.
2. Granfeldt Østgård LS, Medeiros BC, Sengeløv H, et al. Epidemiology and clinical significance of secondary and therapy-related acute myeloid leukemia: a national population-based cohort study. *J Clin Oncol.* 2015;33:3641-3649.
3. Appelbaum FR, Gundacker H, Head DR, et al. Age and acute myeloid leukemia. *Blood.* 2006;107:3481-3485.
4. Juliusson G, Antunovic P, Derolf Å, et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. *Blood.* 2009;113:4179-4187.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Acute Myeloid Leukemia. Version 2.2018. August 1, 2018. www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed September 21, 2018.
6. Irish W, Ryan M, Gache L, et al. 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;33:519-527.
7. Vyxeos (daunorubicin and cytarabine) liposome for injection [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals; August 2017.
8. Mayer LD, Harasym TO, Tardi PG, et al. Ratiometric dosing of anticancer drug combinations: controlling drug ratios after systemic administration regulates therapeutic activity in tumor-bearing mice. *Mol Cancer Ther.* 2006;5:1854-1863.
9. Tardi P, Johnstone S, Harasym N, et al. In vivo maintenance of synergistic cytarabine:daunorubicin ratios greatly enhances therapeutic efficacy. *Leuk Res.* 2009;33:129-139.
10. Lim WS, Tardi PG, Dos Santos N, et al. Leukemia-selective uptake and cytotoxicity of CPX-351, a synergistic fixed-ratio cytarabine:daunorubicin formulation, in bone marrow xenografts. *Leuk Res.* 2010;34:1214-1223.
11. Kim HP, Gerhard B, Harasym TO, et al. Liposomal encapsulation of a synergistic molar ratio of cytarabine and daunorubicin enhances selective toxicity for acute myeloid leukemia progenitors as compared to analogous normal hematopoietic cells. *Exp Hematol.* 2011;39:741-750.
12. Feldman EJ, Lancet JE, Kolitz JE, et al. First-in-man study of CPX-351: a liposomal carrier containing cytarabine and daunorubicin in a fixed 5:1 molar ratio for the treatment of relapsed and refractory acute myeloid leukemia. *J Clin Oncol.* 2011;29:979-985.
13. Lancet JE, Uy GL, Cortes JE. 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;36:2684-2692.
14. Kolitz JE, Strickland SA, Cortes JE, et al. Efficacy by consolidation administration site: subgroup analysis of a phase III study of CPX-351 versus 7+3 in older adults with newly diagnosed, high-risk acute myeloid leukemia (AML). Poster presented at the American Society of Clinical Oncology Annual Meeting; June 2-6, 2017; Chicago, IL.
15. Hagiwara M, Sharma A, Chung K, Delea TE. Acute myeloid leukemia treatment practice patterns, health care resource utilization, and costs in a US commercially insured population. Poster presented at the 22nd Congress of the European Hematology Association; June 22-25, 2017; Madrid, Spain.
16. Lancet JE, Uy GL, Cortes JE, et al. Final results of a phase III randomized trial of VYXEOS (CPX-351) versus 7+3 in older patients with newly diagnosed high-risk (secondary) AML. Abstract presented at the American Society of Clinical Oncology Annual Meeting; June 3-7, 2016; Chicago, IL. Abstract 7000.