Published in final edited form as:

Pediatr Blood Cancer. 2015 October ; 62(10): 1775–1781. doi:10.1002/pbc.25569.

Comparison of In-Patient Costs for Children Treated on the AAML0531 Clinical Trial: A Report From the Children's Oncology Group

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Abstract

Background—A better understanding of drivers of treatment costs may help identify effective cost containment strategies and prioritize resources. We aimed to develop a method for estimating inpatient costs for pediatric patients with acute myeloid leukemia (AML) enrolled on NCI-funded Phase III trials, compare costs between AAML0531 treatment arms (standard chemotherapy ± gemtuzumab ozogamicin (GMTZ)), and evaluate primary drivers of costs for newly diagnosed pediatric AML.

Procedure—Patients from the AAML0531 trial were matched on hospital, sex, and dates of birth and diagnosis to the Pediatric Health Information Systems (PHIS) database to obtain daily billing data. Inpatient treatment costs were calculated as adjusted charges multiplied by hospital-specific cost-to-charge ratios. Generalized linear models were used to compare costs between treatment arms and courses, and by patient characteristics.

Results—Inpatient costs did not differ by randomized treatment arm. Costs varied by course with stem cell transplant being most expensive, followed by Intensification II (cytarabine/

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Additional supporting information may be found in the online version of this article.

Conflicts of Interest Statement: T. A. A. reported serving as a consultant to Hologic and Swiss Precision Diagnostic. B. F. reported research funding from Merck and Pfizer unrelated to this project. R. K. reported serving as a member of a CVS Caremark advisory board regarding subject matters outside of this study. The remaining authors declare no conflicts of interest.

mitoxantrone) and Induction I (cytarabine/daunorubicin/etoposide). Room/board and pharmacy were the largest contributors to inpatient treatment cost, representing 74% of the total cost. Higher AML risk group ($P = 0.0003$) and older age ($P < 0.0001$) were associated with significantly higher daily inpatient cost.

Conclusions—Costs from external data sources can be successfully integrated into NCI-funded Phase III clinical trials. Inpatient treatment costs did not differ by GMTZ exposure but varied by chemotherapy course. Variation in cost by course was driven by differences in duration of hospitalization through room/board charges as well as increased clinical and pharmacy charges in specific courses. *Pediatr Blood Cancer*

Keywords

acute myeloid leukemia; cost and cost analysis; pediatric; treatment cost

INTRODUCTION

Over the past several decades, cooperative oncology group clinical trials for pediatric acute myeloid leukemia (AML) have improved overall survival rates to nearly 65% through intensive chemotherapy regimens that necessitate lengthy hospitalizations. [1–6] However, none have assessed the economic cost of delivering AML chemotherapy. Comparisons of cost between treatment arms have not been performed for any pediatric cooperative group Phase III clinical trial and are infrequently assessed in adult cooperative group oncology trials.[7–9] Interpretation of clinical trial outcomes in the context of cost is of significant interest to patients, providers, policy makers, and payers. A more complete understanding of the drivers of pediatric AML treatment costs may help to identify effective cost containment strategies and prioritize resources. Thus, establishing an accurate and efficient methodology for estimating adjusted costs would substantively augment NCI-funded cooperative group Phase III trials.

Gemtuzumab ozogamicin (GMTZ), an anti-CD33 immunoconjugate, received accelerated FDA approval in 2000 for the treatment of relapsed AML based on Phase II trials that reported single agent overall response rates of approximately 30%.[10] A subsequent post-approval study in adults failed to demonstrate improvement in remission rates and found significantly higher induction mortality for GMTZ + standard chemotherapy relative to chemotherapy alone, leading to the withdrawal of GMTZ from the US market in 2010.[11] More recently, a meta-analysis of five Phase III studies concluded that GMTZ added to standard chemotherapy significantly improved event free survival (EFS) in adult patients with AML and similar results were reported for a Phase III Children's Oncology Group (COG) trial (AAML0531).[1,12] The meta-analysis results led to a call for reconsideration of GMTZ approval in the United States.[13] Given the improved EFS for patients treated with GMTZ on the AAML0531 trial, we sought to determine the economic impact of this treatment.

The objectives of this study were to develop a methodology for estimating inpatient costs for patients enrolled on an NCI-funded cooperative oncology group Phase III clinical trial and to use the methodology to compare costs between treatment arms for AAML0531.

METHODS

Study Population

Between August 2006 and June 2010, AAML0531 enrolled children and adolescents with new-onset AML. Patients were randomized to standard chemotherapy $\pm$ GMTZ (Supplemental Figure).[1] Patients enrolled on AAML0531 who were treated at hospitals contributing to the Pediatric Health Information System (PHIS) were considered in this cost analysis.

PHIS is an administrative database containing inpatient, emergency department, ambulatory surgery, and observation data from 43 not-for-profit, tertiary care pediatric hospitals in the US, representing 85% of freestanding children's hospitals (www.chca.com). Each patient in PHIS is assigned a unique identifier allowing records to be longitudinally linked. The methods for the merging of AAML0531 COG data with daily billing data from PHIS were described previously.[14] Briefly, a list of patients enrolled on AAML0531 generated by COG statisticians was matched on hospital, date of diagnosis, date of birth, and sex to a list of PHIS patients identified as having an ICD-9-CM code for AML (205.xx).

Patients who were enrolled on AAML0531 but subsequently determined not to meet inclusion criteria, enrolled at one of three PHIS centers that did not submit cost-to-charge ratios, or who were not admitted to a PHIS hospital during the on-protocol period were excluded.

Course Definitions

The start of each treatment course was defined as the first day on which chemotherapy was administered and continued until either the start of the subsequent course or the AAML0531 off-protocol date.

Covariates

Patient information including age at enrollment (<1 year, 1 to <5 years, 5 to <10 years, 10 to <15 years and ≥ 15 years), sex, race (white or non-white), insurance status (private, government, or other), AML risk classification (high, intermediate, or low), and minimal residual disease percentage were obtained from the COG AAML0531 database.

PHIS Adjusted Inpatient Costs

Volumes of services, wage- and price-adjusted charges for each unit of service, and department-specific ratio of cost-to-charge (RCC) for each hospital were obtained from PHIS. Adjusted inpatient treatment costs were calculated by multiplying the adjusted charge by the relevant RCC then further adjusted to 2011 US dollars using the consumer price index. Costs for each day of hospitalization were summarized into the following categories: room and board, pharmacy, laboratory, clinical (e.g., respiratory, rehabilitative services, etc.), supply, and imaging. Commercial GMTZ supplies were utilized on AAML0531, thus hospitals billed for the drug and these costs are included in pharmacy costs (mean daily cost for GMTZ: \$2,609 $\pm$ 1,677). Adjusted overall cost and total costs for each category were calculated for each patient as the sum of the daily costs during the entire on-protocol period.

Similar calculations were performed separately for each course. Mean cost per inpatient day was calculated for each patient as the total cost for the given period (entire on-protocol period or specific course) divided by the number inpatient days in the given period. The current analyses include direct medical costs, with the exception of provider, surgery and procedure fees, accrued during inpatient admissions to PHIS hospitals. Indirect costs, outpatient costs, and costs accrued at non-PHIS hospitals were not captured.

Statistical Analyses

Distributions (frequencies and percent) of patient characteristics were calculated by treatment for the current study population as well as the full AAML0531 patient population for those included and not included in cost analyses. Distributions were compared using χ^2 tests. Overall survival (OS) and EFS with 95% confidence intervals (CIs) were estimated using the Kaplan–Meier method and were compared using the log-rank statistic. Cox proportional hazards regression was used to estimate hazard ratios (HRs) with 95% CIs. Course duration and number of inpatient days were summarized as median (range) and compared by treatment using Wilcoxon rank sum tests.

PHIS adjusted inpatient treatment costs (for the entire on-protocol period and by course), were summarized in box-and-whisker plots. Due to the skewed nature of the cost data, generalized linear models with a log link and gamma distribution were used to calculate the crude and adjusted cost ratios (CR) with corresponding 95% CIs, for comparisons of total inpatient cost per patient by treatment arm, between courses, and by remission status (Induction II only), and for comparisons of daily cost per patient between courses, and by treatment arm and patient characteristics. Robust variance estimates were obtained using generalized estimating equation methods with an exchangeable correlation matrix to account for clustering by hospital. Each covariate described above was added independently to the crude model, and the change in the cost ratio was assessed. A change >10% was considered evidence of meaningful confounding. Based on the similarity of estimates between crude and adjusted models, there was no evidence of confounding; thus, the results of crude models are presented. All statistical analyses were performed using SAS (version 9.2, SAS Institute, Inc., Cary, NC). A two-sided P -value <0.05 was used as the threshold for statistical significance.

RESULTS

Thirty-nine percent ($n = 416$) of patients on AAML0531 ($n = 1,070$) were enrolled at PHIS institutions, of which 96% ($n = 378$) were matched and had PHIS data available.[14] Twelve patients identified in PHIS were excluded from the cost analyses because they did not meet AAML0531 inclusion criteria ($n = 2$), were enrolled at a PHIS hospital that did not submit cost-to-charge ratios ($n = 5$), were discharged from a PHIS hospital on the date of AAML0531 enrollment ($n = 2$), or were only admitted to a PHIS hospital after the last date of on-protocol follow-up ($n = 3$). Therefore, the current study population included 366 patients with daily billing data available for at least one course: 47% were randomized to standard chemotherapy and 53% were randomized to standard chemotherapy + GMTZ.

There were no significant differences in sex, age, race, insurance status, or risk classification distributions between treatment groups for the subset of AAML0531 patients included in this cost analysis (Supplemental Table I). The covariate distributions and three-year OS and EFS among AAML0531 patients included in this analysis were comparable to those among patients who were not included (Supplemental Table II). The observed hazard ratio comparing EFS between treatment arms among the subpopulation included in the current cost analyses (HR = 0.85, 95%CI: 0.63, 1.14) was consistent with that observed for the full AAML0531 study population (HR = 0.83, 95%CI: 0.70, 0.99).[1] These results suggest that our study subpopulation is representative of the full AAML0531 population.

Overall and Course-Specific Costs

The total adjusted costs per patient overall and for each course were comparable for the GMTZ and standard arms (Fig. 1). Likewise, neither the course duration nor the number of inpatient days differed by treatment (Table I). However, there were substantial differences in cost between specific chemotherapy courses (Figures 1 and 2).

Stem cell transplant (SCT) was associated with the highest inpatient cost across all courses (Figures 1 and 2). Mean total cost per patient for SCT was significantly higher than for Intensification II (CR = 2.36, 95%CI: 1.96, 2.84) and Intensification III (CR = 2.84, 2.41, 3.35), due to the longer duration of hospitalization (43 vs. 34 days, $P < 0.001$) and corresponding increase in room and board costs as well as higher daily pharmacy and clinical costs (Fig. 2).

The mean costs per patient were significantly higher for Intensification II (CR = 1.51, 95%CI: 1.41, 1.62) and Intensification III (CR = 1.39, 95%CI: 1.25, 1.54) compared to Intensification I (Fig. 2). This difference was attributed to the difference in the number of inpatient days for each course (25 vs. 34 days, $P < 0.0001$) resulting in an increase in total room and board costs.

Inpatient cost for Induction I was significantly higher than for Induction II (CR = 1.60, 95%CI: 1.50, 1.70). While the higher overall cost associated with Induction I was due in part to greater room and board costs associated with a longer median duration of hospitalization (30 vs. 25 days, $P < 0.0001$), assessments of costs per inpatient day that account for differences in duration of hospitalization (Fig. 2, Panel B) still showed significantly greater laboratory (CR = 2.44, 95%CI: 2.10, 2.83), pharmacy (CR = 1.74, 95%CI: 1.58, 1.93), and clinical (CR = 1.57, 95%CI: 1.36, 1.81) expenditures for Induction I versus Induction II.

Component Costs

Distributions of component costs did not differ by treatment (Table II). Overall, room and board was the principle component accounting for approximately 53% of the total cost per patient of on-protocol treatment. Despite the significant variability in total cost per patient by course, the principle drivers of cost were similar across courses (Fig. 2).

Predictors of Cost Per Inpatient Day

While daily costs per patient did not differ by treatment group, sex, race, or insurance status, older age and higher risk classification were each independently associated with higher daily cost (Table III).

DISCUSSION

By merging clinical trial and billing data, we are able to estimate adjusted inpatient costs of AML chemotherapy on AAML0531, a NCI-funded phase III pediatric cooperative group clinical trial. AAML0531 evaluated standard intensive chemotherapy $\pm$ GMTZ for *de novo* AML and found similar OS, but significantly improved EFS through a reduced risk for relapse with GMTZ compared to standard therapy alone.[1] The current analyses demonstrate that overall and course-specific inpatient treatment costs as well as the distribution of component costs were comparable between treatment arms. Thus, the addition of GMTZ to standard pediatric AML therapy improved EFS without an observed increase in inpatient treatment cost.

These results have important implications for clinical practice. In light of recent calls for the reintroduction of GMTZ in the US and its continued use in Europe and Japan, our findings provide reassurance that a decision to make GMTZ available to pediatric patients with AML will not increase health care expenditures. [12,13,15] Additionally, these data demonstrate that a biologically targeted therapy can be added to intensive chemotherapy without increasing inpatient supportive care costs. Thus, payers and national health systems may make decisions regarding provision of adjuvant biologic therapies based on the cost of the biologic itself rather than costs of associated supportive care.

Although inpatient treatment costs for AML did not differ by study arm, there was significant variability in cost by course. Mean adjusted inpatient cost per patient of Induction I was 60% higher than Induction II, a difference likely due to higher patient acuity at diagnosis with subsequent longer hospitalizations and greater pharmacy and laboratory resource utilization. There were also large differences in the inpatient cost of the post-induction courses with SCT having the highest cost followed by Intensification II (cytarabine/mitoxantrone). Mean inpatient costs for SCT were up to 3-fold greater than other post-induction chemotherapy, and averaged over \$260,000 per patient, an estimate that is consistent with other reports.[16,17]

Despite the significant variability in costs across courses, the distributions of the component costs were similar. Room and board during long hospital stays was the primary cost driver in the treatment of AML, representing 45–62% of course-specific costs. Bed charges have been consistently identified as the largest contributor to direct medical costs for treatment of cancer in children and adults.[16–22] Pediatric patients with AML traditionally remain hospitalized during treatment courses until ANC recovery to reduce infectious complications. However, studies suggest that outpatient management is safe and feasible for low-risk adult and pediatric patients with AML.[23–26] Furthermore, studies assessing the outpatient management of febrile neutropenia in adult and pediatric cancer populations and home chemotherapy treatment for pediatric ALL demonstrate reduced costs and improved

quality of life for patients and their families.[27–31] In this context, our results suggest that judicious use of outpatient management may have distinct advantages, including cost savings. Work is ongoing to determine the relative risks and potential costs savings of outpatient AML management.

Consistent with prior cost prediction analyses, we observed older age and higher risk classification to be associated with higher daily cost.[16,17] These findings are compatible with the increased treatment-related mortality in older patients and use of SCT in high risk patients, and thus provide further validation to the cost data. The absence of differences in inpatient cost by race, gender, and insurance status is heartening particularly given the previously reported racial disparities in pediatric AML outcomes and extensively described impact of race, gender, and insurance status on outcomes in adults with malignancy.[32–37]

The merger of PHIS cost data with an NCI-funded randomized trial establishes an enhanced data set that leverages the specific strengths of the individual sources. First, COG clinical trial data, particularly diagnostics, risk classification, and remission status, are unsurpassed in quality. Second, inpatient costs from PHIS are very reliable as these data are used routinely by member hospitals for billing, fiscal planning, and practice optimization.[38] Finally, the merging process and estimation of patient level costs is more efficient and potentially more broadly applicable than methods previously used by others, such as applying single institution cost data to multicenter trials or abstraction of costs from case report forms.[39,40]

Despite these strengths, several limitations should be recognized. Although patients with PHIS inpatient cost data were a representative sample of the AAML0531 trial, the lack of cost data on all study subjects reduces the precision of cost estimates. Non-PHIS institutions, specifically non-freestanding pediatric hospitals and non-US sites, may have different cost structures than PHIS institutions. While pediatric AML therapy is administered in the inpatient setting and treatment complications typically require hospitalization, outpatient costs are potentially important and are unmeasured in this analysis. Work is ongoing to merge COG data with other administrative databases. These data sources will expand the number of patients with cost data and allow for assessment of treatment costs in both the inpatient and outpatient settings. Finally, these analyses are limited to direct hospital costs and do not include physician fees, procedure costs, or other costs carried by patients and families. Further methodological work is needed to develop an efficient process for the acquisition of such data.

This study demonstrates the feasibility of merging NCI-funded cooperative oncology group clinical trial data with inpatient costs from a secondary source and allowed for the comparison of the costs across AAML0531 trial treatment arms. The addition of GMTZ to standard chemotherapy did not impose additional supportive care or inpatient cost, while improving EFS. The methodology employed in this study can be adapted to other NCI trials. Additionally, these results can inform clinicians and hospital administrators on the components of inpatient costs. Specifically for children with AML, these data indicate that inpatient costs are driven by room/board and pharmacy charges and that these costs are

highest in SCT. Our findings also suggest that AML therapy costs may be decreased with selective use of outpatient management.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

National Institutes of Health; Grant number: NIH R01 CA165277 (PI: Aplenc).

Abbreviations

ALL	acute lymphoblastic leukemia
AML	acute myeloid leukemia
ANC	absolute neutrophil count
CI	confidence intervals
COG	Children's Oncology Group
CR	cost ratios
EFS	event free survival
GMTZ	gemtuzumab ozogamicin
HR	hazard ratios
NCI	National Cancer Institute
OS	overall survival
PHIS	Pediatric Health Information Systems
RCC	ratio of cost-to-charge
SCT	stem cell transplant
US	United States

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Fig. 1.

Comparisons of overall and course-specific PHIS adjusted costs per patient by treatment arm. The horizontal lines that form the top and bottom of each box are the 75th and 25th percentiles, respectively. The horizontal line that intersects the box is the median. The whiskers present the 5th and 95th percentiles. The solid squares represent the mean values. Cost Ratios compare cost by treatment regimen (standard + GMTZ vs. standard). Abbreviations: GMTZ = gemtuzumab ozogamicin; SCT = stem cell transplant; CI = confidence interval.

A. Mean Total Cost Per Patient **B. Mean Daily Cost Per Patient** **Fig. 2.**

Distribution of component costs by treatment course. The treatment course-specific pie graphs are sized proportional to their mean total cost per patient (Panel A) and mean daily cost per patient (Panel B).

TABLE I

Course Duration and Total Number of Inpatient Days

Course	Treatment	Course Duration, days				Inpatient Days		
		n	Median	Range	P-value ^a	Median	Range	P-value ^a
Induction I	Standard + GMTZ	187	36	(1–61)	0.9885	30	(1–54)	0.2352
	Standard	169	36	(1–58)		29	(1–52)	
Induction II	Standard + GMTZ	176	34	(24–108)	0.3375	25	(9–72)	0.4987
	Standard	151	34	(7–69)		25	(6–46)	
Intensification I	Standard + GMTZ	163	37	(21–81)	0.9068	25	(1–53)	0.7595
	Standard	136	36	(1–99)		25	(1–99)	
Intensification II	Standard + GMTZ	115	53	(8–175)	0.0565	35	(7–110)	0.1518
	Standard	99	48	(6–121)		33	(6–97)	
Intensification III	Standard + GMTZ	90	44	(27–125)	0.1591	34	(11–89)	0.1853
	Standard	87	41	(9–89)		33	(9–72)	
Stem Cell Transplant	Standard + GMTZ	31	108	(29–126)	0.4862	43	(29–124)	0.4051
	Standard	24	106	(34–168)		43	(29–158)	

GMTZ, gentuzumab ozogamicin.

^a P-values for comparison between treatment regimens (standard + GMTZ versus standard).

TABLE II

Component Costs Per Patient for the Entire On-Protocol Period

Department	Overall Cohort ^a (n = 366)	Standard + GMTZ ^a (n = 194)	Standard ^a (n = 172)	Cost Ratio ^b (95% CI)	P-value ^c
Room & board	187,232 (102,715) [1,673–590,803]	186,648 (98,640) [1,673–508,144]	188,799 (107,858) [2,041–590,803]	1.00 (0.91, 1.13)	0.8081
Pharmacy	80,313 (72,860) [0–656,110]	78,463 (60,070) [0–357,428]	82,700 (58,174) [0–656,110]	0.95 (0.78, 1.17)	0.6379
Lab	41,259 (27,599) [2,342–160,719]	42,792 (28,024) [2,342–157,656]	39,879 (27,244) [3,539–160,719]	1.04 (0.91, 1.21)	0.5020
Clinical	24,482 (52,871) [0–490,002]	24,669 (52,263) [0–490,002]	22,993 (49,770) [0–435,391]	1.07 (0.77, 1.48)	0.7003
Supply	10,498 (21,393) [0–216,156]	8,762 (16,348) [0–111,747]	12,613 (26,052) [0–216,156]	0.84 (0.63, 1.11)	0.2102
Imaging	6,064 (5,754) [0–44,242]	6,132 (5,692) [0–44,241]	6,075 (5,900) [0–33,462]	1.00 (0.86, 1.16)	0.9844

GMTZ, gemtuzumab ozogamicin.

^a Presented as mean (standard deviation) [range];

^b Cost ratio for comparison between arms (standard + GMTZ versus standard);

^c P-values for comparison between arms (standard + GMTZ versus standard).

TABLE III

Comparisons of Mean Adjusted Inpatient Cost Per Day Per Patient by Patient Characteristics

Characteristic	Cost Per Day Mean (sd)	Crude Cost Ratio (95%CI)	P-value ^a
Treatment Regimen			
Standard + Gemtuzumab	2,983 (1,501)	0.95 (0.88, 1.03)	0.2038
Standard	3,175 (1,485)	1 (reference)	
AML Risk Classification ^b			
High	3,563 (1,730)	1.30 (1.13, 1.51)	0.0004
Intermediate	3,068 (1,536)	1.11 (1.02, 1.20)	0.0125
Low	2,677 (940)	1 (reference)	
Sex			
Female	2,953 (1,507)	0.94 (0.87, 1.01)	0.1043
Male	3,199 (1,486)	1 (reference)	
Age ^c , years			
<1	2,604 (1,346)	1 (reference)	
1 to <5	2,757 (1,505)	1.04 (0.88, 1.24)	0.6280
5 to <10	2,970 (1,076)	1.09 (0.91, 1.31)	0.3436
10 to <15	3,427 (1,837)	1.29 (1.09, 1.53)	0.0029
15+	3,369 (1,238)	1.27 (1.08, 1.50)	0.0036
Race			
Non-white	2,898 (1,320)	0.94 (0.83, 1.07)	0.3315
White	3,139 (1,515)	1 (reference)	
Insurance			
Public	2,972 (1,350)	0.99 (0.89, 1.09)	0.7725
Other	2,861 (1,372)	0.95 (0.71, 1.26)	0.7040
Private	3,179 (1,603)	1 (reference)	

sd, standard deviation; CI, confidence interval.

^a P-values for comparison between arms (standard + GMTZ versus standard);^b Linear trend with increasing AML risk classification, $P = 0.0003$;^c Linear trend with increasing age, $P < 0.0001$.